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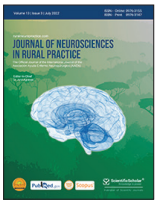

Review Article

Guidelines for pharmacotherapy in Alzheimer's disease – A primer on FDA-approved drugs

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ABSTRACT

The growing prevalence of dementia makes it important for us to better understand its pathophysiology and treatment modalities, to improve the quality of life of patients and caregivers. Alzheimer's disease (AD), a neurodegenerative disease, is the most common form of amnestic dementia in the geriatric population. Pathophysiology of AD is widely attributed to aggregation of amyloid-beta (Aβ) plaques and hyperphosphorylation of tau proteins. Initial treatment modalities aimed to increase brain perfusion in a non-specific manner. Subsequent therapy focused on rectifying neurotransmitter imbalance in the brain. Newer drugs modify the progression of the disease by acting against aggregated Aβ plaques. However, not all drugs used in therapy of AD have been granted approval by the United States Food and Drug Administration (FDA). This review categorizes and summarizes the FDA-approved drugs in the treatment of AD in a manner that would make it a convenient reference for researchers and practicing physicians alike. Drugs that mitigate symptoms of dementia may be categorized into mitigators of Behavioral and Psychological Symptoms of Dementia (BPSD), and mitigators of cognitive decline. BPSD mitigators include brexpiprazole, an atypical antipsychotic with a once-daily dosage suited to treat agitation in dementia patients, and suvorexant, an orexin receptor antagonist used to treat sleep disturbances. Cognitive decline mitigators include cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine and glutamate inhibitors such as memantine. Donepezil is the most commonly prescribed drug. It is cheap, well-tolerated, and may be prescribed orally once daily, or as a transdermal patch once weekly. It increases ACh levels, enhances oligodendrocyte differentiation and also protects against Aβ toxicity. However, regular cardiac monitoring is required due to reports of cardiac conduction side effects. Rivastigmine requires a twice-daily oral dosage or once-daily replacement of transdermal patch. It has fewer cardiac side effects than donepezil, but local application-site reactions have been noted. Galantamine, in addition to improving cognitive symptoms in a short span of time, also delays the development of BPSDs and has minimal drug-drug interactions by virtue of having multiple metabolic pathways. However, cardiac conduction disturbances must be closely monitored for. Memantine, a glutamate regulator, acts as an anti-Parkinsonian agent and an antidepressant, in addition to improving cognition and neuroprotection, and requires a once-daily dosage in the form of immediate-release or sustained-release oral tablets. Disease-modifying drugs such as aducanumab and lecanemab reduce the Aβ burden. Both act by binding with fibrillary conformations of Aβ plaques in the brain. These drugs have a risk of causing amyloid-related imaging abnormalities, especially in persons with ApoE4 gene. Aducanumab is administered once every 4 weeks and lecanemab once every 2 weeks. The decision on the choice of the drug must be made after considering the availability of drug, compliance of patient (once-daily vs. multiple doses daily), cost, specific comorbidities, and the risk-benefit ratio for the particular patient. Other non-pharmacological treatment modalities must also be adopted to have a holistic approach toward the treatment of AD.

Keywords: Alzheimer's disease treatment, Dementia, United States Food and Drug Administration, Brexpiprazole, Lecanemab

INTRODUCTION

The global prevalence of dementia as estimated by the World Health Organization is more than 55 million, and it is predicted to rise to 152.8 million by 2050.[1] With the emergence of this "dementia epidemic," it becomes vital to understand its pathogenesis, symptomatology, and management modalities to enable a better quality of life among patients and caregivers.

Dementia is defined as a clinical syndrome of cognitive decline that is sufficient to cause impairment in activities of daily living.[2] Based on differing clinical and pathological changes, types of dementia may include Alzheimer's disease (AD) dementia, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson's disease dementia (PDD), Huntington's disease dementia, Creutzfeldt-Jakob disease dementia, alcohol-associated dementia, and mixed dementia. Among these, AD is the most common type of dementia in the aging population.[3]

AD is a progressive neurodegenerative disorder predominantly affecting individuals aged ≥65 years. It usually presents as an amnestic disorder, with a subsequent decline in all other cognitive domains.[4] Patients also experience a group of

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Received: 03 July 2023 **Accepted:** 06 September 2023 **Epub Ahead of Print:** 07 October 2023 **Published:** 10 November 2023 **DOI:** 10.25259/JNRP_356_2023

heterogeneous clinical features known as behavioral and psychological symptoms of dementia (BPSD). These include anxiety, agitation, apathy, anhedonia, irritability, delusions, hallucinations, elation, aberrant motor changes, and sleep or appetite changes.[5]

Pathophysiology of AD is widely attributed to aggregation of amyloid-beta (Aβ) plaques, hyperphosphorylation of tau proteins, formation of neurofibrillary tangles, and microglial activation. These neurodegenerative processes lead to synaptic toxicity, neuroinflammation, and neurovascular damage, resulting in cognitive decline.[6-8]

Treatment of AD initially focused on non-specific enhancement of brain perfusion and neuronal activity, involving drugs such as piracetam, dihydroergotoxine, and pyritinol.[9] Subsequent drugs aimed to rectify neurodegeneration-induced neurotransmitter imbalance in the brain. For instance, anticholinesterase drugs such as tacrine, rivastigmine, galantamine, and donepezil increase acetylcholine (ACh) levels in the cortex, and NMDA receptor-antagonists like memantine protect neurons against excess activity of glutamate.[10,11] Physicians, therefore, have a wide armamentarium of pharmacologically-diverse drugs at their disposal, to administer to patients with AD. However, not all drugs have been granted approval by the United States Food and Drugs Administration (FDA). This review aims to comprehensively describe the FDA-approved drugs for symptom-mitigation and disease-modification in AD and to serve as a "ready-reckoner" for practicing physicians. The drugs have been categorized according to their outcome of intent, addressed symptom, and subsequently by their mechanism of action in a manner that would make this review a convenient reference for researchers and practicing physicians alike.

SYMPTOM-MITIGATING DRUGS

Drugs for behavioral and psychological symptoms of dementia

Brexpiprazole (Rexulti®)

The FDA announced the supplemental approval for the use of brexpiprazole (Rexulti®), an atypical antipsychotic, in the treatment of agitation associated with dementia in AD on May 11, 2023.

Pharmacokinetics and pharmacodynamics

Brexpiprazole is chemically and pharmacologically related to aripiprazole. It is a 5-HT_{1A}, D_2, and D_3 partial agonist and a 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, and α_{2C} antagonist. It has an oral bioavailability of 95% and reaches peak plasma concentrations within 4 h after consumption. It takes 10–12 days to attain steady-state concentrations in the body and has a high protein-binding that is unaffected by kidney or liver impairment.[12] The latest randomized controlled trials show that 2 mg/day fixed dose of brexpiprazole shows the best efficacy in the treatment of BPSDs, specifically agitation.[13]

Mechanism of action

Due to its action on both dopaminergic and serotonergic receptors, the drug reduces neuronal excitability and also leads to improvement of mood in patients with BPSDs. Brexpiprazole has potent binding at serotonergic and α1B receptors, thereby mitigating the extrapyramidal symptoms associated with antipsychotic drugs. It also causes less sedation, due to reduced binding at H1-receptors.[14]

Adverse effects

Most adverse effects noted in clinical trials on the use of the drug in BPSDs were mild-to-moderate and included nasopharyngitis, headache, dizziness, urinary tract infection, insomnia, and somnolence. Serious adverse effects observed in a few patients included agitation and QTc interval prolongation.[13] However, the odds of mortality as found in a meta-analysis were relatively high with respect to placebo (odds ratio 2.22; 95% confidence interval).[15] In addition, cognitive impairment, dystonia, akathisia, neutropenia, and agranulocytosis should be closely monitored, while on treatment with brexpiprazole.

Suvorexant (Belsomra®)

Suvorexant (Belsomra®), an orexin receptor-antagonist originally developed for the management of insomnia, was approved by the FDA in 2020 for treating sleep disturbances in mild-to-moderate AD.[16]

Pharmacokinetics and pharmacodynamics

The time taken for absorption of the drug is 2 h. It has a $t_{1/2}$ of 12 h, which is longer than that of other commonly used sedative-hypnotics. It is extensively metabolized in the liver by CYP3A with a minor contribution from CYP2C19 to pharmacologically inactive hydroxyl-suvorexant. Elimination is through feces and to a lesser extent, urine. The FDA-approved dosage of 5 mg, 10 mg, 15 mg, and 20 mg is to be taken orally, 30 min before sleep.[16]

Mechanism of action

Individuals suffering from AD have been found to have high levels of orexin in the cerebrospinal fluid, a neurotransmitter known to promote wakefulness. This impairs nocturnal sleep, leading to the development of insomnia.[17] The neurotransmitters orexin-A and orexin-B, released by

orexin neurons present in the lateral hypothalamic region, peri-fornical region, and posterior hypothalamus are mediated by orexin-1 and orexin-2 receptors. Orexin-B only interacts with orexin-2 receptors, which have been found to be majorly responsible for wakefulness by activating the tuberomammillary nucleus histaminergic neurons. Orexin A has an additional role to play in the sleep-wake cycle by interacting with both the receptors-1 and -2. Suvorexant, a dual orexin receptor-antagonist, blocks the action of both orexin-1 and -2 receptors, thereby helping in the initiation and maintenance of sleep.[18]

Adverse effects

The most common adverse effect was somnolence.[19] Other common adverse effects of the drug include diarrhea, xerostomia, upper respiratory tract infection, headache, dizziness, fatigue, dyspepsia, and peripheral edema.[20] The drug is contraindicated in patients suffering from narcolepsy with cataplexy.

Cognitive symptoms

Cholinesterase inhibitors

Donepezil (Aricept®)

Donepezil (Aricept®) is the first second-generation non-competitive, reversible acetylcholinesterase (AChE) inhibitor that was approved by the FDA in 1996 for use in mild, moderate, and severe AD dementia. It is also among the most commonly prescribed drugs in patients with AD.

Pharmacokinetics and pharmacodynamics

Donepezil has a relatively high systemic bioavailability of 86.8% and takes 3–4 h to reach peak plasma concentrations.[21] It has a $t_{1/2}$ of 70 h, making it suitable for once-daily dosing.[22] Studies have found 5 mg and 10 mg once-daily doses to be effective in reducing tau-protein expression, decreasing hippocampal atrophy, lowering serum Aβ levels, and improving cognitive performance in patients of AD.[21] A higher-dose preparation (23 mg) has also been approved by FDA for the use in patients with moderate-to-severe AD.[23] At present, there is FDA approval for immediate-release (1996), orally disintegrating (2004) and sustained-release tablets (2010), as well as a transdermal patch (2022). The transdermal once-weekly patch delivers the drug at 5 mg/day, with fewer systemic adverse effects.

Mechanism of action

It reversibly binds with AChE, thereby reducing the hydrolysis of ACh in the synapse and improving cholinergic neurotransmission.[23] Donepezil also activates the phosphatidylinositol-3-kinase/Akt route and enhances oligodendrocyte differentiation, reducing Aβ-induced toxicity as an outcome.[24] It also activates the sigma1 receptor and protects against Aβ toxicity by regulating calcium signaling, cellular defense, and neurotransmitter release.[25]

Adverse effects

The drug is generally well-tolerated. Transient cholinergic side effects such as nausea, vomiting, diarrhea, weight loss, fatigue, insomnia, anorexia, and asthenia may be seen in patients. Caution must be exercised in patients with peptic ulcer disease, urinary tract obstruction, chronic obstructive pulmonary disease, asthma, or seizure disorders. The discontinuation rate due to adverse effects was found to be around 10%.[26] In addition, reports of cardiac side effects such as QT-prolongation, symptomatic bradycardia, and polymorphic ventricular tachycardia necessitate regular cardiac monitoring in patients.[27]

Rivastigmine (Exelon®)

Rivastigmine (Exelon®) is a cholinesterase inhibitor approved by the FDA in 2000, in the treatment of AD and Parkinson's disease.[28]

Pharmacokinetics and pharmacodynamics

Rivastigmine exhibits a dose-response relationship, with higher doses of the drug demonstrating greater efficacy.[29] It can be administered orally and by transdermal patch. Clinical studies have demonstrated the symptomatic efficacy of oral rivastigmine across all stages of AD and mild-to-moderate PDD. Extensive, saturable first-pass metabolism leads to the bioavailability of the administered oral dose being approximately 35%. On the other hand, pharmacokinetic studies of the rivastigmine patch have confirmed that transdermal administration prolongs t_{max}, lowers C_{max}, and reduces the fluctuation of plasma drug concentrations compared with oral administration.[30,31] The drug is metabolized completely, with primarily renal elimination. The principal metabolite of rivastigmine exhibits a minimum of ten-fold reduction in activity against AChE compared to the parent drug.[32] The half-life of rivastigmine is 1.5 h and it is cleared by kidneys at the rate of 2.1–2.8 L/h. It has been demonstrated in single-dose pharmacokinetic studies that the metabolism of the drug is not significantly affected by the concurrent administration of digoxin, which is a commonly prescribed antiarrhythmic and anti-failure drug in geriatric patients. The capsule comes in 1.5 mg, 3 mg, 4.5 mg, and 6 mg doses and is administered twice daily. The transdermal patch comes in different sizes (5 cm^2, 10 cm^2, 15 cm^2, and 20 cm^2) with different rates of drug delivery (4.6 mg, 9.5 mg, 13.3 mg, and 17.4 mg over 24 h, respectively). The patch,

which is replaced every day, reduces the prevalence of side effects, especially nausea and vomiting.[33]

Mechanism of action

It is a slow reversible dual inhibitor of AChE and butyrylcholinesterase, selective for the G1 isoform of AChE. This mechanism enhances cholinergic function and improves mental functions such as memory and thinking. It does not exhibit hepatic metabolism.[31,34] As the disease progresses and fewer cholinergic neurons remain functionally intact, there may be a reduction in the effect of rivastigmine.[35]

Adverse effects

Adverse effects include diarrhea, tremors, blurred vision, weight loss, nausea, and confusion. Application-site reaction with transdermal patch has been noted. Contraindications include known hypersensitivity to rivastigmine and other carbamate derivatives, known peptic ulcer disease, active gastrointestinal bleeding, cardiac conduction defects, sick sinus syndrome and bradyarrhythmia, asthma or chronic obstructive pulmonary disease, bleeding ulcer, and seizure history or risk.[36] Patients must be monitored for cardiac side effects.

Galantamine (Razadyne®)

Galantamine (Razadyne®) received FDA approval in 2001 for the treatment of mild-to-moderate AD. It is well-tolerated and is known to improve function, cognition, and activities of daily living in a very short span of time (around 6 months) in patients with mild-to-moderate AD. BPSDs are delayed, and caregiver burden is minimized due to the use of this drug.[37]

Pharmacokinetics and pharmacodynamics

Galantamine is a tertiary alkaloid identified in the early 1950s and derived from the plant, *Galanthus nivalis*. It is currently available as a synthetic formulation. Galantamine has predictable linear elimination kinetics at the recommended maintenance doses of 16 and 24 mg/day, and a relatively short $t_{1/2}$ of approximately 7 h. It is administered twice daily as a tablet, and once daily in the morning as an extended-release capsule. A dosage of 24 mg/day has been shown to be consistently effective in large multicentric trials for the functional, cognitive, and behavioral symptoms associated with AD when compared with a placebo.[38] In addition, it has a relatively high bioavailability. The drug has extensive hepatic metabolism through different pathways, by the cytochrome P450 enzymes CYP2D6 and CYP3A4, thus carrying a low risk for clinically relevant drug-drug interactions.[39]

Mechanism of action

Being a reversible competitive inhibitor of AChE, the drug causes the accumulation of ACh in the brain. It also potentiates the action of ACh on nicotinic receptors, resulting in a net increase in the cholinergic neurotransmission in the central nervous system, and facilitating treatment. Galantamine has been proven in short-term, double-blind, and placebo-controlled studies to generate modest gains in cognitive tests among individuals diagnosed with mild-to-moderate AD.[40]

Adverse effects

Galantamine, being a cholinesterase-inhibitor, has a tendency to elicit gastrointestinal symptoms such as nausea, vomiting, diarrhea, and loss of appetite on starting treatment, along with exacerbation of these symptoms on increasing the dosage.[41] It may lead to urinary retention and sinus bradycardia due to the cholinergic effects of the drug, and the initial treatment entails stopping the offending medication and administering atropine intravenously. Patients should be monitored closely for seizures. All patients should be regarded as having a high chance of experiencing cardiac conduction disturbances. Administration of galantamine necessitates alertness and careful consideration of risk factors that may cause syncope, delirium, and QT-prolongation.[42]

Glutamate regulators

Memantine (Namenda®)

Memantine (Namenda®) received FDA approval in 2003 for the treatment of moderate-to-severe AD. It is an adamantine hydride-derived primary aliphatic amine.

Pharmacokinetics and pharmacodynamics

Memantine is well-absorbed when administered orally. Peak drug concentrations are attained in 3–7 h. It exhibits linear pharmacokinetics when administered at normal therapeutic doses. Food does not interfere with drug absorption. It is primarily cleared by active tubular secretion in the kidneys, with 48% of the administered dose being excreted unchanged and 52% being metabolized to the minimally active N-glucuronide conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine. The clearance is moderated by tubular reabsorption, which is pH-dependent. It has a $t_{1/2}$ of 60–70 h and is suitable for once-daily dosing. It is available in oral immediate-release and sustained-release formulations.[43] It is a low-to-moderate affinity uncompetitive (open-channel) NMDA receptor-antagonist which binds preferentially to NMDA receptor-operated cation channels.

Mechanism of action

Memantine primarily acts by blocking current flow through channels of the glutamatergic NMDA receptors and inhibiting the influx of calcium into cells that occur as a result of chronic, glutamate-induced NMDA receptor activation.[43] It has a role as an NMDA receptor-antagonist, neuroprotective agent, antiparkinsonian drug, dopaminergic agent, and antidepressant. High doses of memantine inhibit mechanisms of synaptic plasticity which underlie learning and memory processes. Lower, clinically useful concentrations help enhance synaptic plasticity in the brain, thereby improving memory and protecting against excitotoxicity.[43]

Adverse drug effects

Memantine was found to be safe and well-tolerated. Frequently reported mild adverse effects included agitation, dizziness, fall, accidental injury, influenza-like symptoms, headache, and diarrhea.[44] It should be avoided in patients with hypersensitivity to memantine hydrochloride.

DISEASE-MODIFYING DRUGS

Aducanumab (Aduhelm®)

Aducanumab (Aduhelm®), which received approval in 2021, is the first FDA-approved pharmacological modality for AD that acts by reducing Aβ-burden.[45] It has reported positive results in phase III drug trials.[46]

Pharmacokinetics and pharmacodynamics

Studies have shown favorable pharmacokinetic parameters.[47,48] Aducanumab exhibits a long duration of action and is administered once every 4 weeks.[49] It is available as a clear-to-opalescent and colorless-to-yellow solution in single-dose vials for intravenous (IV) infusion. It is diluted with 100 mL of 0.9% sodium chloride and administered based on the subject's body weight**.** It is recommended that the first and second doses be 1 mg/kg infusions, third and fourth 3 mg/kg, fifth and sixth 6 mg/kg, and subsequent infusions be 10 mg/kg body weight.[50] As an Aβ-directed monoclonal antibody, it binds to Aβ, leading to a reduction in amyloid plaques in the brain. Pharmacodynamic studies have revealed that aducanumab binds to fibrils and facilitates their removal by microglial cells, by disrupting the bridge between them.

Mechanism of action

Aducanumab is a monoclonal immunoglobulin gamma (IgG)-1 monoclonal antibody.[51] It crosses the blood–brain barrier and selectively targets the soluble oligomers and insoluble fibrillary conformations of Aβ-plaques in the brain, thus slowing disease progression. This selective binding distinguishes it from other immunotherapeutic agents targeting Aβ.[52,53] It is presently approved for use in patients with mild cognitive impairment or mild AD. No drug-drug interactions are currently reported. Aducanumab may be used concomitantly with other medications utilized to manage AD.[51]

Adverse effects

The most common adverse events observed are amyloid-related imaging abnormalities (ARIA). Aducanumab is associated with a significantly higher rate of ARIA compared to the rates observed in placebo groups or natural history studies. Among those receiving the drug, ARIA manifesting as brain edema or effusion (ARIA-E) and hemorrhage (ARIA-H) were most commonly observed in ApoE4 gene carriers (43%) and least often in those without the ApoE4 gene (20.3%). No contraindications have yet been reported. All potential side effects in patients treated with aducanumab, especially falls, headache, and diarrhea, should be taken into consideration.[50] Routine magnetic resonance imaging (MRI) monitoring for ARIA must be undertaken.

Lecanemab (Lequembi®)

Lecanemab (Lequembi®), an IV anti-AD drug, has been granted accelerated approval by the FDA in January 2023. It is the second drug (after aducanumab) targeting the pathophysiology of the disease to be approved in the treatment of AD.

Pharmacokinetics and pharmacodynamics

The drug reaches a steady-state concentration after 6 weeks of starting therapy. The mean value of the central volume of distribution at a steady state is 3.22 L. The drug is degraded by proteolytic enzymes in the same manner as endogenous IgGs and has a $t_{1/2}$ of 5–7 days. Lecanemab of 10 mg/kg administered every 2 weeks was found to cause a significant reduction in the aggregation of amyloid plaques. A significant increase in Aβ 42/40 levels was noted every 2 weeks.[54] There was also a significant decrease in plasma p-tau 181 when administered with the drug as compared to the placebo group. There were no other significant findings with respect to the dosage of the medicine in AD patients.[55]

Mechanism of action

Lecanemab is a humanized monoclonal antibody that has a high-affinity binding to the soluble Aβ-protofibrils, which are considered to be neurotoxic. The drug reduces Aβ-fibril aggregation in astrocytes, leading to a reduction in

amyloid plaques, resulting in clinical benefits and disease-modification. It has been tested in persons with early AD and has been shown to reduce markers of amyloid deposition. The decline in measures of cognition and function at 18 months was moderately-less as compared to placebo. However, it was associated with adverse-events.[56] Plasma biomarkers such as Aβ42/40 and p-tau181 have been found effective in monitoring the effects of lecanemab treatment.[55]

Adverse effects

The most common adverse effect noticed in patients treated with lecanemab was the development of ARIA-E and ARIA-H. Mild-to-moderate severity of ARIA symptoms which consisted of headache, nausea, mental confusion, vomiting, tremors, and gait disturbances was typically noticed within the first 3 months of lecanemab administration and was dose-dependent.[57,58] One study, further, suggested that the risk of developing ARIA was more in ApoE4 gene carriers on receiving the highest dosage.[59] At present, there are no contraindications to the use of this drug. Routine MRI monitoring for ARIA must be undertaken.

SUMMARY

Drugs that mitigate symptoms of dementia may be categorized into mitigators of BPSD and mitigators of cognitive decline. BPSD mitigators include brexpiprazole, an atypical antipsychotic with a once-daily dosage suited to treat agitation with minimal side effects, and suvorexant, an orexin receptor-antagonist used to treat sleep disturbances. Cognitive decline mitigators include cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine and glutamate inhibitors such as memantine. Donepezil is the most commonly prescribed drug. It is cheap and well-tolerated and may be prescribed orally once-daily, or as a transdermal patch once-weekly. It increases ACh levels, enhances oligodendrocyte differentiation, and also protects against Aβ-toxicity. However, regular cardiac monitoring is required due to reports of cardiac conduction side effects. Rivastigmine requires twice-daily oral dosage, or once-daily replacement of transdermal patch. It has fewer cardiac side effects than donepezil, but local application-site reactions have been noted. Galantamine, in addition to improving cognitive symptoms in a short span of time, also delays the development of BPSDs and has minimal drug-drug interactions by virtue of having multiple metabolic pathways. However, cardiac conduction disturbances must be closely monitored for. Memantine, a glutamate regulator, acts as an anti-Parkinsonian agent and an antidepressant in addition to improving cognition and neuroprotection and requires once-daily dosing in the form of immediate-release or sustained-release oral tablets. Disease-modifying drugs such as aducanumab and lecanemab reduce the Aβ-burden. Both act by binding with fibrillary conformations of Aβ-plaques in the brain. These intravenously administered drugs have a risk of causing ARIA, especially in persons with ApoE4 gene, and require routine MRI monitoring. Aducanumab is administered once every 4 weeks and lecanemab once every 2 weeks.

CONCLUSION

With the growing number of individuals affected with AD, it becomes imperative to focus on developing new, effective treatment modalities. However, it is important to bear in mind that the adverse effects of anti-AD drugs may be distressing to the patient, and life-threatening in some instances. Availability of drug, compliance of patient (once-daily vs. multiple doses daily), cost, specific comorbidities, and the risk-benefit ratio for the particular patient must be taken into account by the physician before prescribing anti-AD drugs. Regular monitoring for serious adverse effects must be undertaken to ensure the safety of the patient. Non-pharmacological interventions dealing with cognitive symptoms and BPSDs, such as cognitive training, non-invasive brain stimulation techniques, Snoezelen therapy, music, and massage therapy must also be considered. Given the complex and multifaceted nature of the disease, a holistic and patient-centric approach to treatment must be adopted. Clinicians must be sensitive to the "wants" as much as the "needs" of their patients so that the affected individuals have greater autonomy over their treatment plan and the quality of life they lead.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Varadharajan A, Davis AD, Ghosh A, Jagtap T, Xavier A, Menon AJ, *et al*. Guidelines for pharmacotherapy in Alzheimer's disease – A primer on FDA-approved drugs. J Neurosci Rural Pract 2023;14:566-73.