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Review

Limitations of Alzheimer's Disease Medications

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ABSTRACT

Alzheimer's disease is an irreversible, progressive brain disorder affecting more than 6.5 million Americans that slowly destroys memory and thinking skills and, eventually, the ability to carry out simple tasks. While the specific causes of Alzheimer's are not fully known, it is characterized by changes in the brain-including amyloid beta plaques and neurofibrillary, or tau tangles that result in the loss of neurons and their connections. These changes affect a person's ability to remember and think. Individual responses to Alzheimer's medications can vary. Some people may experience significant cognitive benefits, while others may have a more modest response or no response at all. The cognitive benefits provided by some medications are generally temporary. The medication may slow down the rate of cognitive decline, but it does not stop the progression of Alzheimer's disease. Some medications are more effective in the early and moderate stages of Alzheimer's disease. This article in brief described the limitations of the drugs that are used in the treatment of Alzheimer's disease.

Keywords: Alzheimer's disease, Medications, Adverse effects, Dementia

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, a major cause of disability and mortality among older adults in the US.[1] A 5-year delay in the onset of AD, corresponding to a 50% reduction in incidence rates, would reduce the prevalence by 41% in 2050.[2,3] Cerebrospinal fluid and blood biomarkers are being rapidly developed to facilitate early diagnosis of AD and identify AD-related brain changes at early stages.[4] In addition to biomarkers solely for AD risk stratification, it is critical to identify modifiable risk factors that are involved in AD etiology and neuropathology.

Current therapeutic agents for Alzheimer's disease–related dementia temporarily improve symptoms but do not alter the underlying disease course.[5,6] Some evidence suggests that amyloid removal slows the progression of disease.[7] One anti-amyloid antibody (aducanumab) has received accelerated approval from the Food and Drug Administration. Lecanemab is a humanized monoclonal antibody that binds with high affinity to soluble amyloid-beta (Aβ) protofibrils, which have been shown to be more toxic to neurons than monomers or insoluble fibrils.[8-18]

Conventional Pharmacologic Treatment for Cognitive Symptoms

ChE Inhibitors (Donepezil, Rivastigmine, and Galantamine)

The ChE inhibitors all have the indication for the treatment of dementia of the Alzheimer's type. Guidelines for the treatment of AD recommend the use of ChE inhibitors as a valuable treatment for AD and the use of memantine for moderate-to-severe AD. None of the ChE inhibitors have been compared in head-to-head studies, so the decision to use one over another is based on differences in mechanisms of action, adverse reactions, and titration schedules.[19-21]

Treatment should begin as early as possible in patients with a diagnosis of AD. Patients should be switched to another ChE inhibitor from their initial ChE inhibitor if they show an initial lack of efficacy, initially respond to treatment but lose clinical benefit, or experience safety/ tolerability issues. This switch should not be attempted until the patient has been on a maximally tolerated dose for a period of 3 to 6 months. The switch should also be based on realistic expectations of the patient and/or caregiver. ChE inhibitor therapy should be discontinued in patients who experience poor tolerance or adherence, who show a lack of clinical improvement after 3 to 6 months at optimal dosing, who continue to deteriorate at the pretreatment rate, or who demonstrate dramatic clinical deterioration following initiation of treatment.[22-25]

Donepezil

Donepezil is a piperidine ChE inhibitor, which reversibly and noncompetitively inhibits centrally active acetyl-cholinesterase. Donepezil is approved for the treatment of dementia of the Alzheimer's type at a dose of 5 mg/day. This dose should be increased to 10 mg/day if needed after 4 to 6 weeks. Efficacy has been demonstrated in patients with mild-to-moderate and -severe AD. Adverse reactions with donepezil include nausea, vomiting, and diarrhea. Only a small number of drug interactions have been reported with donepezil. In vitro studies show a low rate of binding of donepezil to cytochrome P450 (CYP)3A4 or 2D6. Whether donepezil has the potential for enzyme induction is not known. Monitoring for possible increased peripheral side effects is advised when adding a CYP2D6 or 3A3/4 inhibitor to donepezil treatment. Also, inducers of CYP2D6 and 3A4 could increase the rate of elimination of donepezil.[26-28]

Rivastigmine

Rivastigmine has a central activity for both the acetylcholinesterase and butyrylcholinesterase enzymes. Acetylcholinesterase is found in two forms: globular 4 and globular 1. In postmortem studies, globular 4 is significantly depleted, while globular 1 is still abundant. Thus, blocking the metabolism of globular 1 may lead to higher concentrations of Ach. Rivastigmine has higher activity at globular 1 than at globular 4. Theoretically, this may be advantageous, as rivastigmine prevents the degradation of Ach via the acetylcholinesterase globular 1 over the course of the disease as compared to the other ChE inhibitors.

The dual inhibition of acetylcholinesterase and butyrylcholinesterase may lead to broader efficacy. As acetylcholinesterase activity decreases with disease progression, the acetylcholinesterase selective agents may lose their effect, while the dual inhibitors may still be effective due to the added inhibition of butyrylcholinesterase. However, this has not been demonstrated clinically.[29]

Rivastigmine is approved for the treatment of mild-to-moderate dementia of AD at an initial dose of 1.5 mg twice daily; if this dose is tolerated for at least 2 weeks, then the dose can be increased to 3 mg twice daily. Increases to 45 m twice daily and 6 mg twice daily should be attempted only after at least 2 weeks at the previous dose. Tolerability and absorption are improved when the dose is given with food. Rivastigmine is also available in a patch formulation, with an initial dose of 4.2 mg/24 hours applied once daily. The maintenance dose of the patch is 9.5 mg/24 hours applied once daily. A minimum of 4 weeks

of treatment and good tolerability with the previous dose should be observed before consideration of an increase in dose. When switching from the oral formulation to the patch, if the patient is taking less than 6 mg/day of oral, then the 4.2 mg/24-hour patch is recommended. If the patient is taking 6 to 12 mg/day of oral, then the 9.5 mg/24-hour patch is recommended. The first patch should be applied on the day following the last oral dose. Cholinergic side effects are common with rivastigmine, but are usually well tolerated if the recommended dosing schedule is followed. If side effects cause intolerance, several doses can be held, then dosing can be restarted at the same or the next lower dose. There are no pharmacokinetic drug interactions with drugs metabolized via CYP1A2, 2D6, 3A4/5, 2E1, 2C9, 2C8, or 2C19. Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine.[30]

Galantamine

Galantamine is a ChE inhibitor, which elevates Ach in the cerebral cortex by slowing the degradation of Ach. It also modulates the nicotinic Ach receptors to increase Ach release from surviving presynaptic nerve terminals. In addition, it may increase glutamate and serotonin levels. The clinical benefit of the action of these additional neurotransmitters is unknown. Galantamine is approved for the treatment of mild-to-moderate dementia of AD. It can be dosed once or twice daily (if using the immediate-release tablet or extended-release capsule). The initial dose is 8 mg daily (or 4 mg twice daily) for 4 weeks. If tolerated the dose can be increased if needed to 16 mg daily (or 8 mg twice daily) for at least 4 weeks. Again, if this dose is tolerated, the dose can be increased if needed to 24 mg daily (or 12 mg twice daily).[31] The adverse reactions associated with galantamine are similar to those observed with the ChE inhibitors. CYP3A4 and 2D6 are the major enzymes involved in the metabolism of galantamine. Pharmacokinetic studies with inhibitors of this system have resulted in increased galantamine concentrations or reductions in clearance. Similarly to donepezil, if inhibitors are given concurrently with galantamine, monitoring for increased cholinergic side effects should be done.[32]

NMDA Receptor Antagonist

Memantine

Memantine is a noncompetitive antagonist of the NMDA type of glutamate receptors, which are located ubiquitously throughout the brain. It regulates activity throughout the brain by controlling the amount of calcium that enters the nerve cell, a process essential for establishing an environment required for information storage. Overstimulation of the NDA receptor by excessive glutamate allows too much calcium into the cell, disrupting information processing. Blocking NDA receptors with memantine may protect neurons from the effects of excessive glutamate without disrupting normal neurotransmission.

Memantine is indicated for the treatment of moderate-to-severe dementia of the Alzheimer's type. The initial dose is 5 mg/day with increases to 20 mg/day if needed, with a minimum of 1 week between dosage increases. Doses greater than 5 mg/day should be given in two divided doses. A suggested titration is 5 mg/day for at least 1 week, 5 mg twice daily for at least 1 week, 15 mg/day (5 mg in the morning and 10 mg in the evening) for at least 1 week, and then 10 mg twice daily. If the patient has a creatinine clearance of 3 4 29 mL/min, then the target dose should be 5 mg twice daily. It is likely to be given as monotherapy but can be given in combination with ChE inhibitors. Adverse reactions associated with memantine include constipation, confusion, dizziness, headache, coughing, and hypertension. Extra monitoring should be done if memantine is given concurrently with a ChE inhibitor. In vitro studies have shown that memantine produces minimal inhibition of CYP450 enzymes CYP1A2, 2A6, 2C9, 2D6,

2El, and 3A4. These data indicate that no pharmacokinetic interactions with drugs metabolized by these enzymes should be expected.[33-35]

Nonconventional Pharmacologic Treatment

Many other nonconventional treatments have been used as adjunctive treatments during AD. Vitamin E has often been recommended for use as an adjunctive treatment because of its antioxidant properties. It has potential effectiveness, a favorable side-effect profile, and low cost. The maintenance dose of vitamin E should be titrated to 1,000 IU twice daily. However, a recent meta-analysis suggests that high doses (greater than 400 IU/day of vitamin E should be avoided due to increased all-cause mortality. Estrogen has been investigated for use in AD, but as mentioned previously, was associated with an increased risk of dementia. Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been investigated for their place in the therapy of AD. There is a lack of convincing data and significant adverse effects (gastritis and GI bleeds) associated with their use, so they are not recommended for general use in the treatment or prevention of AD at this time. Statins (3-hydroxy-3-methyleglutaryl-CoA reductase inhibitors) should be reserved for those patients who have other indications for their use. Ginkgo biloba has also been studied for its potential use in AD. Until this product has a more standardized manufacturing process and until its long-term safety and efficacy are established, it should be recommended with caution.[36-40]

DISCUSSION

Individual responses to donepezil can vary. Some people may experience significant cognitive benefits, while others may have a more modest response or no response at all. The cognitive benefits provided by donepezil are generally temporary. The medication may slow down the rate of cognitive decline, but it does not stop the progression of Alzheimer's disease. It is typically more effective in the early and moderate stages of Alzheimer's disease. Its impact may be limited in the later stages when significant neurodegeneration has occurred. It may not substantially improve a person's ability to perform everyday tasks independently. The cost of donepezil and other Alzheimer's medications can be a limitation, particularly for individuals without adequate insurance coverage.[41] The postmarketing report of Donepezil includes abdominal pain, agitation, aggression, cholecystitis, convulsions, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, rash, rhabdomyolysis, QTc prolongation, Stevens-Johnson syndrome toxic epidermal necrolysis and torsade de pointes.[42]

The postmarketing reports of Rivastigmine include tachycardia, abnormal liver function tests, hepatitis, Seizure, aggression, nightmares, allergic dermatitis, application site hypersensitivity (patch), blister, disseminated allergic dermatitis, Stevens-Johnson syndrome, and urticarial.[43]

The postmarketing report of Galantamine includes hallucinations, seizures, and extrapyramidal disorder, while the postmarketing report of Memantine includes agranulocytosis, leukopenia (including neutropenia), pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura, cardiac failure congestive, pancreatitis, hepatitis, suicidal ideation, Acute renal failure (including increased creatinine and renal insufficiency), Stevens-Johnson syndrome.[44,45]

Lecanemab-irmb was approved on January 6, 2023, using the Accelerated Approval pathway, under which the FDA may approve drugs for serious conditions where there is an unmet medical need and a drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. The results of a Phase 3 randomized, controlled clinical trial to confirm the drug's clinical benefit have recently been reported.[46]

To offer Lecanemab treatment, tertiary centres must have access not only to MRI facilities to exclude individuals with certain vascular comorbidities and to monitor safety but also to PET facilities or labs that can analyse the CSF biomarkers indicative of Alzheimer's disease. The list of infrastructure and human resources needed for the drug to be used safely is extensive. According to appropriate use recommendations from an expert group based in the USA, a multidisciplinary team of health professionals must work cooperatively. The FDA has warned about the limited data available on patients exposed to antithrombotic medications and the expert group recommends that people on anticoagulants (eg, warfarin and direct oral anticoagulants) should not receive Lecanemab, as their risk of developing cerebral haemorrhage could be too high. Nevertheless, periodic MRI monitoring of those eligible for treatment is essential to detect amyloid-related imaging abnormalities (ARIAs) that can result in severe side effects, such as brain oedema. Centres must develop protocols for the management of rare but severe complications, which adds intensive care units to the list of necessary resources. Adding another layer of complexity to management and clinical decision-making, during Lecanemab treatment the risk of ARIA increases in a gene dose-dependent manner for carriers of the *APOE* ε4 allele. Hence, there is also a need for genotyping resources and genetic counseling.[47]

CONCLUSION

Essential elements in the treatment of AD include education, communication, and planning with the family caregiver of the patient. Treatment options, legal and financial decisions, and the course of the illness need to be discussed with the patient and family members. In this regard, the clinician's emphasis should be on helping to maintain a therapeutic living environment while minimizing the burden of care resulting from the disease.

Conflict of Interest

The authors declare no conflicts of interest relevant to this article.

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