INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: Alzheimer's Disease
-May 2023-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a clinical review of Alzheimer's Disease (AD) at the Spring meeting held on April 25-26th, 2023. Current medication(s) listed on the IHS National Core Formulary (NCF) relevant to this condition include donepezil and memantine. Following clinical and pharmacoeconomic review, as well as utilization trend analysis, the NPTC made **no modifications to the NCF**.

AD is a progressive neurodegenerative disorder of uncertain cause and pathogenesis primarily affecting older adults. It is the most common cause of dementia and the leading source of morbidity and mortality in the aging population. Although the etiology and pathophysiology of the disease is not fully understood, the most extensively studied concept of AD involves the amyloid hypothesis. The accumulation of amyloid protein plaques and the formation of tau protein tangles are associated with neuronal atrophy and negatively impact a person's ability to remember and think normally. Common symptoms of AD include confusion, disorientation, low mood or anxiety, memory impairment, difficulty in performing self-care tasks, and difficulty in speech or language.[1]

Discussion:

Mild Cognitive Impairment (MCI), also known as Mild Neurocognitive Disorder (NCD), is characterized by development of memory impairment with retained ability to perform activities of daily living (ADL). MCI can be the first cognitive expression of AD or secondary to other disease processes.[2] Dementia, also known as Major Neurocognitive Disorder, is a group of disorders characterized by impairment of both memory and capacity to perform ADLs.[3] There are multiple risk factors that can increase an individual's risk for AD including but not limited to: increased age, family history, vascular disease risk factors, as well as lifestyle and genetic factors.[1]

Diagnosis of AD requires a decline in both cognition and function as well as specific neuropathology without evidence of another cause.[1] FDA approved therapies for treatment of AD include the acetylcholinesterase inhibitors (AChEI), an N-methyl-D-aspartate (NMDA) receptor antagonist, and two anti-amyloid monoclonal antibodies.

Therapies for treatment of AD were last reviewed by NPTC in 2019. Although there are new emerging treatment options, all previous recommendations still apply to current clinical practice and AChEI's (donepezil, rivastigmine, or galantamine) and NMDA (memantine) remain the mainstay of AD treatment. AChEI's are recommended as monotherapy for management of mild to moderate AD. Memantine is recommended as monotherapy for managing AD for people with moderate AD who are intolerant of or have a contraindication to AChEI's. Combination therapy can be considered in patients with moderate to severe disease. Frequent reevaluation of clinical benefit is recommended with discontinuation of therapy once the patient is no longer having any benefit or becomes fully dependent.[5] There is an ongoing clinical debate regarding the role of anti-amyloid treatment in AD. Newer FDA approved therapies include anti-amyloid monoclonal antibodies (aducanumab and lecanemab) which were approved via accelerated approval pathway and remain controversial in clinical practice.

The EMERGE and ENGAGE trials, two identical RCT's, included participants aged 50-85 years with a diagnosis of MCI due to AD or mild AD and also had a positive amyloid positron emission tomography (PET) scan. Participants received either low dose (3 or 6 mg/kg) aducanumab or high dose (10 mg/kg) aducanumab vs. placebo. The primary outcome assessed was a change from baseline in the Clinical Dementia Rating (CDR) scale. The primary endpoint was met in EMERGE (difference of -0.39 for high-dose aducanumab vs placebo [95% CI, -0.69 to -0.09; *p*=.012; 22% decrease]) but not in ENGAGE (difference of 0.03, [95% CI, -0.26 to 0.33; *p*=.833; 2% increase]). Both trials were prematurely discontinued based on futility analysis. Study limitations included early study termination, post-hoc analyses for re-evaluation of endpoints, multiple post-hoc subgroup analyses, inconsistent findings, surrogate endpoints with no direct correlation to clinical improvement. The most common adverse event was amyloid-related imaging abnormalities-edema (ARIA-E), occurring at rates of 25.7% (n=140) and 25.4% (n=139) in the EMERGE and ENGAGE low-dose groups, respectively, and rates of 34% (n=186) and 35.5% (n=198) in the EMERGE and ENGAGE high-dose groups, respectively. Comparatively, the placebo group experienced respective ARIA-E rates of 2.2% (n=12) and 3% (n=16) in EMERGE and ENGAGE.[7]

The Clarity AD trial, a multicenter, double-blinded, phase 3 trial included participants 50-90 years of age with early AD (mild CI or mild dementia due to AD) with positive evidence of amyloid PET or by CSF testing in 250 sites worldwide.

Participants received lecanemab IV 10 mg/kg every 2 weeks vs. placebo. The primary outcome assessed was change from baseline at 18 months in the score on the Clinical Dementia Rating-Sum of Boxes (CDR-SB). In terms of cognitive outcomes, this is the first clinical trial of an anti-amyloid antibody to clearly demonstrate that amyloid clearance is associated with a slowing of cognitive decline in participants with early AD (27% relative change in CDR-SB, absolute difference of 0.45 points; change from baseline, 1.21 for lecanemab vs 1.66 placebo; (MD -0.45 95% CI: -0.67 to -0.23; p<0.001, unknown clinical significance). Additionally, the lecanemab group had 49% less decline on European Quality of Life – 5 dimensions (5 level version) at 18 months vs. placebo (p<0.01), 56% less decline on the Quality of Life in Alzheimer's Disease (QOL-AD) in the lecanemab group vs. placebo group (p<0.01), caregivers of participants in the lecanemab group reported 38% less decline on Zarit Burden Interview at 18 months vs placebo (p<0.001) and 23% less decline on the QOL-AD (subject by proxy) compared to placebo (p<0.05).[8] Although rates of ARIA were less than seen in the aducanumab trials, it did still commonly occur.

Notably, the Institute for Clinical and Economic Review recently published the final evidence report on lecanemab for AD and found that current evidence is not adequate to demonstrate a net health benefit with compared to supportive care alone.[8]

Findings:

Guidelines continue to recommend an acetylcholinesterase inhibitor at the time of Alzheimer's dementia diagnosis with consideration of addition of memantine in those with moderate to severe staging or as monotherapy in individuals intolerant to acetylcholinesterase inhibitors. Although there are now additional agents approved for treatment of AD, the clinical debate regarding the role of anti-amyloid treatment in AD remains ongoing and controversial among the medical community. Real world ARIA occurrences and consequences caused by these agents may be more severe if monitoring via MRI does not occur as frequent as in the clinical trials. Furthermore, success in amyloid reduction, at the expense of ARIA, by majority of newer generation anti- Aβ trials stands in contrast with the lack of a corresponding clinical change. Clinicians should keep close attention to the rapidly evolving disease modifying therapies for AD as new data emerges.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:

1. Keene, CD. Epidemiology, pathology, and pathogenesis of Alzheimer disease. UpToDate. Retrieved February 22, 2023
2. Petersen RC, Lopez O, Armstrong MJ. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;16;90(3):126-135.
3. World Health Organization. Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization; 2019.
4. Handbook of Clinical Neurology, Vol. 193 (3rd series). Precision Medicine in Neurodegenerative Disorders, Part II. A.J. Espay, Editor.
5. National Institute for Health and Care Excellence. Dementia: Assessment, management and support for people living with dementia and their careers. London: 2018 Jun. PMID: 30011160.
6. Villain N, Planche V, Levy R. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 1: Meta-analysis and review of efficacy and safety data, and medico-economical aspects. Rev Neurol (Paris). 2022;178(10):1011-30.
7. Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer's Disease (EMERGE and ENGAGE) ClinicalTrials.gov identifier: NCT02484547, NCT02477800, Updated September 2, 2021. Accessed March 3, 2023. https://clinicaltrials.gov/ct2/show/study/NCT02477800
8. van Dyck CH, Swanson CJ, Aisen P. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023 Jan 5;388(1):9-21.
9. Institute for Clinical and Economic Review. Aducanumab for Alzheimer's Disease: Effectiveness and Value. Final Evidence Report and Meeting Summary. August 5, 2021.