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Symptomatic and Promising Disease-Modifying Treatments for Dementia Syndromes

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Dementia could be defined as a range of cognitive and behavioral symptoms, including memory loss, executive dysfunction, and change in personality, and a reduction in a person's ability to carry out daily activities. The most common types of dementia are Alzheimer's disease (AD), vascular dementia, mixed dementia, dementia with Lewy bodies, and frontotemporal dementia (1).

All currently approved treatments for dementia are symptomatic treatments that could influence cognitive and behavioral symptoms without changing the underlying neuropathological progression of the disease (2).

The U.S. Food and Drug Administration (FDA) has approved six drugs for the treatment of Alzheimer's disease. Five of these drugs, including; Donepezil, Rivastigmine, Galantamine, Memantine, and Memantine, combined with donepezil temporarily treat Alzheimer's symptoms by increasing the number of neurotransmitters in the brain nevertheless, could not change the underlying brain changes of Alzheimer's and the course of the disease.(3 ,4). ChE-Is could influence the loss of presynaptic cholinergic cells in the nucleus basalis of Meynert (5).

The sixth drug, aducanumab, was approved by the FDA in June 2021. The first FDA-approved drug to address the underlying biology of Alzheimer's disease rather than the symptoms by reducing beta-amyloid plaques in the brain (6).

The aim of recent drug development trials with disease modification methods will be to prevent or delay the onset of dementia syndromes (7).

In the review of several recent clinical trials, 5-HT6 antagonists have failed to establish a drug-placebo difference in cognitive outcomes in the Phase 3 development programs (8). A nicotine transdermal patch is currently in a Phase 3 trial. On the other hand, GV-971 reverses gut dysbiosis and reduces systemic inflammation, approved by the National Medical Products Administration in China (9).

Some studies have proposed that CPC-201 as a ChE-Is in combination with peripheral cholinergic receptor blockers could result in greater central cholinergic stimulation even though limited peripheral cholinergic side effects (10).

Also, Rotigotine and Rasagiline, with their effect on the dopaminergic system, could produce improvement in executive function in patients with dementia (11).

Medications targeting Ab take advantage of diverse mechanisms, including reducing the generation of Ab42, preventing the aggregation of Ab plaques, or increasing the rate of Ab clearance from the cerebrospinal fluid (CSF) and brain (12).

Nevertheless, the alteration in the methods of dementia-related studies following the recurrent failures of anti-Ab drugs has been described (13). The main reason for the failure could be irreversible neurotoxicity for the Ab level in mild to moderate AD patients. Currently, the new therapeutic approaches have focused on neuroinflammation mediated by microglia and astrocytes in dementia neuropathogenesis instead of the Ab pathologies (14).

For instance, phenolic compounds with antioxidant properties, including oleuropein and epigallocatechin gallate (EGCG) will be considered an effective intervention in dementia treatment (15).

Ultimately, oligomers monoclonal antibodies with promising

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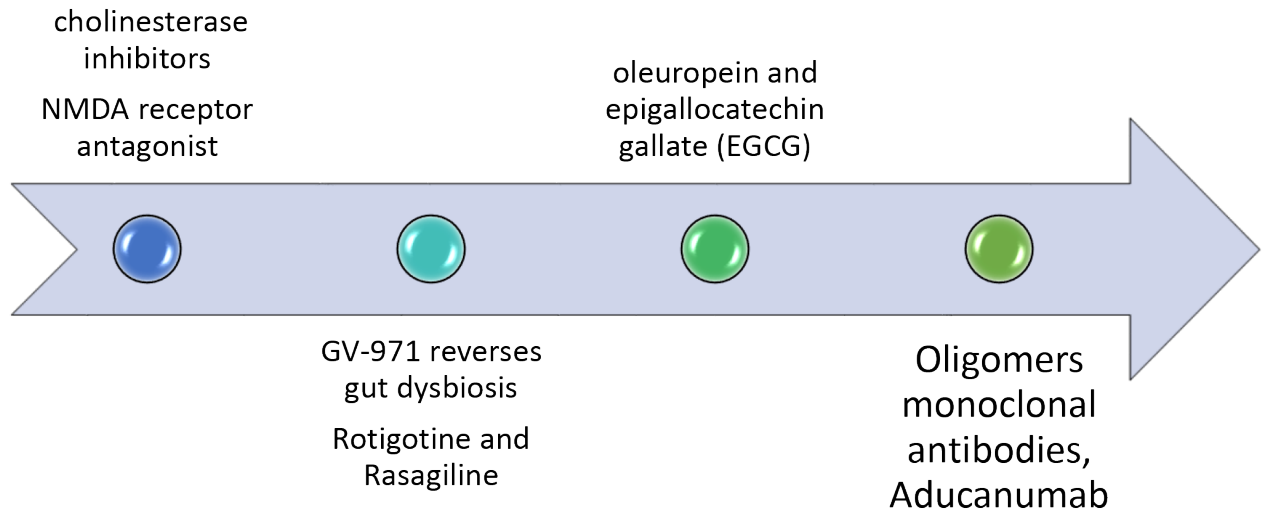
efficacy could bind to insoluble fibrils and soluble Ab protofibrils, thus, relieving the brain's Ab burden with a positive impact on cognition (16).

Aducanumab is an Ab- targeting monoclonal antibody that is currently showing a significant dose-dependent reduction of Ab plaques' size. Besides binding to both forms of Ab, soluble oligomers, and insoluble fibrils, aducanumab also alleviates calcium dys-homeostasis in affected neurons (17).

There are currently no approved treatments for any neuropsychiatric symptom in AD; there is progress in clinical trials and trial methodology, several drugs are in late-stage trials for behavioral disorders in AD or dementia, and one agent has been submitted to the FDA for approval as a treatment for dementia-related psychosis (18). Pimavanserin has been submitted for possible marketing approval by the FDA (19).



Current symptomatic and promising disease-modifying treatments for dementia syndromes

Conclusion

There are no approved therapies for disease modification of any adult-onset neurodegenerative disorder except for Aducanumab. Less progress is currently evident in the development of cognitive-enhancing agents.

As a solution, better trial participant characterization, use of pharmacodynamics biomarkers, and implementation of more sensitive outcomes may result in improving the success of development programs.

Despite decades of research, we are still encountering a lack of significant success in the pharmacotherapy of dementia syndromes, generally according to the multifactorial etiologies of the disorder that can initiate neurodegeneration independently.

At present, combination therapy that simultaneously targets several factors appears promising. However, physicians should consider that Aducanumab is not a cure for Alzheimer's disease and is not appropriate for all individuals living with Alzheimer's disease, and it only could prescribe for Mild Cognitive Impairment or mild dementia due to Alzheimer's disease.

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