Short Communication ISSN 2771-9057

Recent Advances in Clinical Trials

Pamphlet for Relatives of Individuals with Alzheimer's Dementia

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Received: 20 Apr 2025; **Accepted:** 23 May 2025; **Published:** 02 Jun 2025

Citation: Jeffrey Fessel. Pamphlet for Relatives of Individuals with Alzheimer's Dementia Recent Adv Clin Trials. 2025; 5(3); 1-2.

Keywords
Alzheimer's dementia, Relatives, Possible cure, Useful drugs.

ALZHEIMER'S DEMENTIA MIGHT BE CURABLE BY AVAILABLE DRUGS. A pamphlet for family members.

In this brief article, written in mostly non-technical language, family and friends of persons with Alzheimer's dementia, may quickly read about available drugs which might cure the dementia.

The first thing to know is that the combined effects of a small number of factors, from a long list of as many as 20 different ones, may cause the dementia. The factors themselves and their number, differ from patient to patient. The next thing to know is that there may be as many as 25 different drugs needed to address all of those 20 different factors. Even though the dementia of an individual patient might depend upon far fewer than 20 causes, it still would require several drugs to take care of those fewer causes, whereas probably 2 or 3 is the tolerable maximum. The number of drugs that can be used in combination is also limited by the facts that whatever drugs are used must get into the brain in order to be effective, and by the serious consequences of possible interaction drug-drug interactions between the drugs that are used. The following paragraphs will describe the drugs that remain and why they might be used to cure the dementia. The drugs that enter brain include: intranasal insulin (used with edarovone); glucogen-like peptide 1 molecules (GLP-1 agonists) such as dulaglutide, donepezil; lecanemab (also representing aducanumab and donanemab); levodopa; selective serotonin uptake inhibitor (SSRI) such as fluoxetine; roscovitine (used with tamoxifen); and diclofenac (a nonsteroidal anti-inflammatory agent). There are others but these drugs suffice for this pamphlet.

CHAT GPT was asked: are there drug-drug interactions between any two or any three drugs chosen from the above listed drugs. The response indicates that fluoxetine must be eliminated because of serious consequences of its interactions with five of them. Following are brief notes about the remaining drugs.

Intranasal Insulin
In Alzheimer's dementia there is insulin resistance in the brain, therefore impaired ability to utilize glucose, which is the main nutrient for brain neurons. Thus, this depleted neuronal function and that depletion is a major cause of the dementia. Insulin given intranasally provides better brain levels than given subcutaneously. Glucose is mainly stored as glycogen in brain cells called astrocytes, and glycogen is converted to energy if astrocytes degrade glycogen to lactate, which is released and used by neurons.

Edarovone
In Alzheimer's dementia it is not only the changes that initiated the cognitive loss that should be addressed but, critically, the counter-reactions to those changes, that include insulin resistance in brain, causing inadequate metabolism of brain glucose. Edarovone has many beneficial actions. It reduces the level of reactive oxygen species (ROS) that are high in Alzheimer's dementia and contribute to insulin resistance; it decreases production of substances that promote inflammation, which participates in causing dementia; and it protects the cells that line blood vessels in brain and are damaged in Alzheimer's dementia. Edarovone can be used with intranasal insulin.

GLP-1 Agonists
Addressing the dysfunctions of all brain cell types in Alzheimer's dementia should be a curative strategy. GLP-1 agonists would be beneficial because receptors for GLP-1 are present in all of the main brain cell types. Commercially available GLP-1 agonists have mostly shown positive effects upon cognition or no effects.

One important reason for no effects is a reduced rate of entering the brain. Among the available GLP-1 agonists, dulaglutide has the greatest entry to brain and might offer the best likelihood for cure of AD. A study involving almost 9000 subjects used dulaglutide, and showed significant benefit to cognition.

Donepezil

Donepezil is an anticholinesterase drug, so prevents the enzymatic breakdown of acetylcholine, an important neurotransmitter involved in learning and memory, whose levels are significantly reduced in Alzheimer's dementia. Using donepezil has improved cognitive function.

Lecanemab (and the Drugs, Aducanumab and Donanemab, with Similar Effects)

In a large trial, lecanemab slowed clinical decline in Alzheimer's dementia by 27% after 18 months of treatment compared with those who received a placebo. It did not reverse the dementia. An important side effect was temporary brain swelling.

Levodopa

Levels of dopamine are decreased in Alzheimer's dementia and levodopa is a precursor of dopamine. In addition, levodopa increases levels of an enzyme, neprilysin, that breaks down amyloid plaque. Although levodopa crosses the blood brain barrier, as with insulin, levodopa can be administered intranasally to improve entry into the brain, where it activates dopaminergic receptors. Intranasal levodopa is approved by the FDA.

Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) and reduces inflammation. Inflammation of the brain is a major contributor to the cause of Alzheimer's dementia, so use of diclofenac should benefit the possibility of curing the dementia.

Roscovitine

The levels of cyclin-dependent kinase 5 (Cdk5) are increased in the brains both of patients with Alzheimer's dementia and of Alzheimer's dementia model mice, for which inhibition of Cdk5 rescued the Alzheimer's pathology. Active Cdk5 affects many aspects of brain mechanisms, including cognitive functions. A protein called p25 is a major activator of Cdk5; p25 levels and, thus, active Cdk5, were elevated in AD brain; and overexpression of p25 in a transgenic mouse resulted in the formation of phosphorylated tau, neurofibrillary tangles and cognitive deficits, that are all present in human Alzheimer's dementia. ATP supplies energy to cells; roscovitine impairs the ATP binding site of Cdk5, and it decreased Cdk5 activity by 87.2%. Inhibition of Cdk5 activity might, presumptively, cure Alzheimer's dementia.

Tamoxifen

Tamoxifen also binds to the p25 activator of Cdk5; it reduced Ckd5 activity by 84.5%. Inhibition of Cdk5 activity might, presumptively, cure Alzheimer's dementia.

Note to Relatives

You might wish to ask the treating physician for brief comments about these drugs. He or she cannot yet prescribe them until both their safety and efficacy have been established by formal clinical trials.