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# Cholinesterase Inhibitors and Their Impact on the Mentality and Physicality of Alzheimer's Disease Patients

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## Abstract

The increasing prevalence of Alzheimer's Disease (AD) among older adults makes it necessary to create public, comprehensive understandings of its management strategies. This literature review analyzes the role of cholinesterase inhibitors—including donepezil, galantamine, and rivastigmine—in slowing down the cognitive symptoms associated with AD, along with potential emotional side effects that may arise from these medications. Cholinesterase inhibitors are divided into two categories of inhibitors: acetylcholinesterase inhibitors and butyrylcholinesterase inhibitors. Acetylcholinesterase inhibitors block the breakdown of acetylcholine, a key neurotransmitter involved in memory and learning. Donepezil and galantamine fall under this category and are noted for their cognitive benefits. However, they may induce emotional instability, impacting both patients and caregivers. Butyrylcholinesterase inhibitors have been more recently discovered, and they play a role by inhibiting the activity of the enzyme, butyrylcholinesterase, from breaking down acetylcholine and butyrylcholine. Rivastigmine is both an acetylcholinesterase and

butyrylcholinesterase inhibitor, offering a unique transdermal delivery option that may improve tolerability. By understanding the mechanisms, applications, and limitations of cholinesterase inhibitors, healthcare providers and patients can make more informed decisions regarding medication use and prescription for AD management, contributing more care and support for individuals affected by this disease.

*Keywords:* rivastigmine, donepezil, galantamine, Alzheimer's disease, cholinesterase inhibitor

## Introduction

Approximately 6.5 million people in the United States and at least 55 million worldwide, aged 65 and older, are diagnosed with Alzheimer's disease, suffering from a range of symptoms that vary in intensity and severity (Mayo Clinic, 2023). The manifestation of Alzheimer's disease is often characterized by the initial onset of mild memory loss that may eventually progress to more severe forms of cognitive dysfunction (CDC, 2024; Heilman, K. M., & Nadeau, 2022). These advanced forms can be deficits in learning, memory, language, and visuospatial skills, which are attributed to neuropathological changes in the cerebral cortex and limbic system (Corey-Bloom, J., 2002). Alzheimer's disease can additionally peak with loss of physical control and psychosis (Penn Medicine, 2020; Heilman, K. M., & Nadeau, 2022).

More than two hundred known genetic factors are involved in the development of Alzheimer's disease, making it an incredibly complex, multifaceted disorder (Ramón Cacabelos, 2007). Consequently, developing a treatment that can eliminate these constituents

poses a significant challenge. Therefore, many medications primarily aim to restrict the symptoms and factors contributing to Alzheimer's disease (McDade & Bateman, 2017). Most of these medications predominantly aim to delay memory loss, the progression of dementia, and alleviate other notable symptoms. For instance, a specific class of medicines used to stall these symptoms are called cholinesterase inhibitors (Singh & Sadiq, 2023). Cholinesterase inhibitors, also known as acetylcholinesterase inhibitors and butyrylcholinesterase inhibitors, are a class of both pharmaceutical and non-pharmaceutical medications that elevate levels of various enzymes (acetylcholine and butyrylcholinesterase) in the body (Singh & Sadiq, 2023; Trang & Khandhar, 2023; Williams et al., 2019). These medications are commonly used in the management of Alzheimer's disease and other neurological disorders where there is an acetylcholine deficiency (Penn Medicine, 2020; Drugs.com, 2019).

Previous studies and experiments have analyzed the medical effects of cholinesterase inhibitors for Alzheimer's disease patients. This literature review examines the effects of these medications on patients and also explores the emotional impacts of these medications on patients, which may, in turn, improve the quality of life for both patients and their supporting families.

## Overview of Cholinesterase Inhibitors

### Analyzing Donepezil and Galantamine and Their Effects

#### Pharmacological Profile of Donepezil

Donepezil is one of three FDA-approved acetylcholinesterase inhibitors (Langmaid, 2022; Drugbank, 2005a). An oral medication, donepezil is approved to treat all stages of

Alzheimer's disease (Alzheimer's Association, 2019). Like all three acetylcholinesterase inhibitors, donepezil binds to and inactivates acetylcholinesterase to prevent acetylcholine from breaking down (DrugBank, 2005a). While the increase of acetylcholine in the brain can lead to an improvement in memory, learning, and overall cognitive functions, donepezil is shadowed by many physical side effects (Mayo Clinic, 2024a). The most common side effects include diarrhea, loss of appetite, muscle cramps, exhaustion, nausea, and vomiting. Less frequent effects include constipation, fainting, joint pain, unusual bleeding, and others (Mayo Clinic, 2024a).

**Mental and Physical Side Effects of Donepezil**

Donepezil may cause patients to experience irritation, emotional instability, restlessness, aggression, paranoia, and delusions (Hategan & Bourgeois, 2016). Mood swings, depression, and anxiety may worsen the cognitive and behavioral symptoms of Alzheimer's, adding more symptoms like confusion and memory loss. Increased agitation and irritability can lead to difficulties in daily interactions and caregiving, potentially causing stress for both patients and caregivers. However, some individuals, despite other reports of depression, also indicate a trend for elevated mood regardless of their history of depressive disorder. (Hategan & Bourgeois, 2016). Additionally, improvements in cognitive functions like memory and clarity may lead to a better quality of life for the patient.

**Pharmacological Profile of Galantamine**

Galantamine is the second acetylcholinesterase inhibitor primarily used to treat mild to moderate Alzheimer's disease (Thompson, 2001; Mayo Clinic, 2024b). While sustaining its reputation as an acetylcholinesterase inhibitor, galantamine not only inhibits

acetylcholinesterase but also modulates nicotinic acetylcholine receptors (Bourne & Renaud, 2008). This modulation may offer additional cognitive benefits, though the clinical significance of this is still under study. An oral medicine, galantamine causes side effects, but may be a cause for concern if many unwanted effects occur (Mayo Clinic, 2024b; Drugbank, 2005b). These side effects are similar to donepezil; however, individual tolerance and specific side effects can vary between the two drugs. The most common physical side effects include nausea, vomiting, chest pain, dizziness, trembling, and a slow/irregular heartbeat. Rarer effects include blurred vision, confusion, fainting, redness, and troubled breathing (Mayo Clinic, 2024b; Drugbank, 2005b).

### Mental and Physical Side Effects of Galantamine

Among galantamine's list of possible mental side effects are discouragement, feeling sad or empty, irritability, loss of interest or pleasure, and other symptoms of depression (Mayo Clinic, 2024b). Although uncommon, hallucinations can occur, particularly in patients with more advanced disease, and can be distressing (Cunha, n.d.). However, a 2004 research study conducted in Switzerland exploring the behavioral impacts of galantamine on AD patients resulted in improved mood and fewer feelings of anxiety than without the medication (Monsch & Giannakopoulos, 2004). The study showed that galantamine significantly reduced behavioral disturbances over a three-month period, and also lifted many burdens on patient caregivers (Monsch & Giannakopoulos, 2004).

## Butyrylcholinesterase Inhibitors

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Butyrylcholinesterase inhibitors are compounds that prevent the enzyme butyrylcholinesterase (BChE) from breaking down choline-based substrates (Sanz & Calvo, 2021). These substrates include butyrylcholine and acetylcholine (Sanz & Calvo, 2021). Acetylcholine is primarily hydrolyzed by acetylcholinesterase (AChE), but BChE can also hydrolyze the neurotransmitter, especially when AChE levels are low (Sanz & Calvo, 2021; Sam & Bordoni, 2023).

**Functions of Butyrylcholinesterase**

Butyrylcholinesterase (BChE) is a cholinesterase enzyme similar to acetylcholinesterase but with a broader substrate target range (Simmons & Kaczmarek, 2017). It is primarily found in the liver (Mehta et al., 2012). Unlike acetylcholinesterase, which is highly specific for acetylcholine, BChE can hydrolyze a variety of choline-based esters such as acetylcholine and butyrylcholine (a synthetic substrate used in laboratory studies to measure the activity of butyrylcholinesterase) (Williams et al., 2019; Simmons & Kaczmarek, 2017; Ghosh & Reddy, 2004). It hydrolyzes acetylcholine in lieu of AChE, but because AChE is specifically designed to break down acetylcholine quickly and effectively at synaptic clefts and neuromuscular junctions, acetylcholinesterase is more favorably used with respect to its functions (Gambardella et al, 2024; Ghosh & Reddy, 2004). It serves an essential function as a compensatory enzyme in AD, with numerous studies indicating that inhibiting BChE holds significant promise for treating more advanced stages of the condition. (Zhou & Huang, 2022).

## Analyzing Rivastigmine and Its Effects

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## Pharmacological Profile of Rivastigmine

Rivastigmine is both an acetylcholinesterase inhibitor and a butyrylcholinesterase inhibitor that treats predominantly mild to moderate dementia for AD patients (Lakhan, 2024). Rivastigmine also binds to these enzymes to block their activity (Fletcher, 2023). It comes in two forms, a patch and an oral tablet. A 2014 research review suggests that the patch may be better than the pill form for some AD patients because it offers improved tolerability and consistent dosing compared to the pill (Sadowsky et al., 2014). The patch helps reduce gastrointestinal side effects and provides easier support, making it a preferable option for many patients, especially for those who take rivastigmine at higher doses (Sadowsky et al., 2014).

## Mental and Physical Side Effects of Rivastigmine

Though it offers reduced side effects, the chances are not zero. The patch may still cause some side effects, including nausea, headache, weakness, and skin reactions at the patch site. Severe side effects include bloody or black stools and seizures (Fletcher, 2023). The oral route causes similar side effects (except skin irritation), but higher risks of nausea, vomiting, and diarrhea (MedlinePlus, 2019).

Rivastigmine, in rare cases, may cause depression, anxiety, agitation, hallucinations, and confusion (Fletcher, 2023; Sadowsky et al., 2014; Clarke, 2007). Mood swings and irritation are examples of minor emotional instability that patients experience, while depression, anxiety, agitation, and confusion are more severe effects that can affect their emotional well-being. If significant emotional side effects continue, they may interfere with

daily activities, social interactions, and complicate caregiving. However, some subtle benefits include enhancing the quality of life for not only the patient, but for the caregiver as well (Alzheimer Scotland, 2011). Improved mood and easier interactions can contribute to the overall happiness of the family (Alzheimer Scotland, 2011).

## New and Upcoming Cholinesterase Inhibitors

### Historical Overview of Approved Inhibitors

Donepezil was approved for medical use in 1996 and is still utilized as a generic medication today (Ramón Cacabelos, 2007). Shortly after its approval, rivastigmine gained FDA approval in 1997 (Patel & Gupta, 2023). Galantamine was developed as a cholinergic drug in the 1960s and reported to have positive effects in the 1970s, but was officially approved by the FDA for the fight against AD much later in 2001 (Mucke, 2015). Donepezil and rivastigmine are, by far, the most commonly used drugs to slow down memory loss because of their effectiveness and rarity of side effects (Alzheimer's Society, 2023). Because AD is a terminal disease that affects so many worldwide, new cholinesterase inhibitors have been invented but have yet to be approved by the FDA.

### Introduction to ALPHA-1062 (Zunveyl) and Comparative Side Effects

However, one new generation of acetylcholinesterase inhibitor managed to get approval from the FDA in July of 2024. ALPHA-1062, or Zunveyl, is a delayed-release oral medication used to treat mild-to-moderate AD (Meglio, 2024). Zunveyl features a prodrug form of galantamine, which is converted into galantamine once it is absorbed into the body. This conversion happens after it passes through the digestive system, to prevent triggering

adverse gastrointestinal effects (Wexler, 2024). Like galantamine, it boosts levels of acetylcholine, but focuses on making treatment more tolerable for AD patients. Since Zunveyl is a form of galantamine, both drugs have similar side effects. However, because Zunveyl's primary focus is to reduce the prevalence of side effects, the chances of experiencing severe aftereffects are slimmer (Drugs.com, 2025). In three bioequivalence studies with the intention of studying Zunveyl's side effects, less than 2% of adults in these studies reported any gastrointestinal issues (Wexler, 2024; Meglio, 2024). Considering that 20% of adults experience nausea or vomiting as a side effect from the drug galantamine, the FDA preferred this new treatment over the brand-name version, as it provides equivalent levels of galantamine to the body and minimizes physical tolls on the body (Berryhill, 2023; Wexler, 2024).

## Chemical Structures and Functional Mechanisms of Cholinesterase Inhibitors

While donepezil, galantamine, and rivastigmine target cholinesterase enzymes, their chemical compositions reveal differences in functionality and receptor bindings that allow for differences in interactions with cholinesterase. Figure 1 below demonstrates the chemical structures of the three cholinesterase inhibitors, illustrating how each of the treatments' unique structures influences the inhibition of acetylcholinesterase or butyrylcholinesterase.

**Figure 1**

*Chemical Structures of Cholinesterase Inhibitors*

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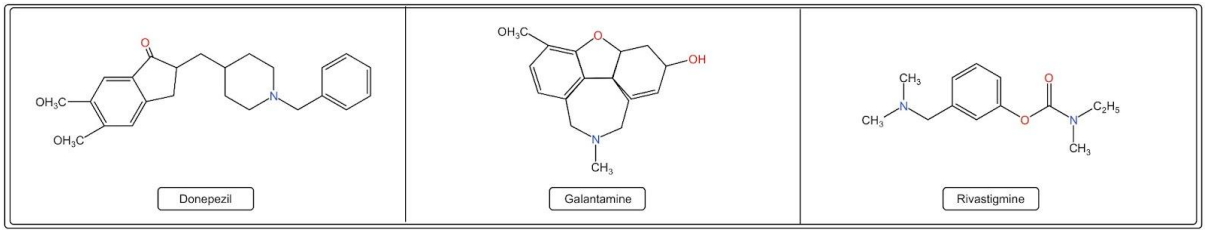


*Note.* Chemical structures of donepezil, galantamine, and rivastigmine. Diagram created by author based on reference images.

## Chemical Structure and Background of Donepezil

Donepezil is chemically known from its IUPAC name as 2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one, showing its piperidine-based structure that permits it to mimic acetylcholine and bind to the anionic site of AChE. This structural feature, also shown in Figure 1, helps stabilize the interaction between the drug and the enzyme, increasing donepezil's binding strength and target focus, or affinity and specificity (Stepankova & Komers, 2008). It acts as a reversible, non-competitive inhibitor of AChE, allowing it to bind to the enzyme without permanently inactivating it. Additionally, its high selectivity for AChE over BChE prevents the chances of peripheral side effects and ultimately raises levels of ACh, dopamine, and noradrenaline outside neurons. By boosting acetylcholine levels in the central nervous system, donepezil indirectly stimulates nicotinic and muscarinic receptors, contributing to cognitive enhancement (Ramón Cacabelos, 2007).

## Chemical Structure and Background of Galantamine

Galantamine, chemically named (4aS,6R,8aS)- 5,6,9,10,11,12- hexahydro- 3-methoxy- 11-methyl- 4aH- [1]benzofuro[3a,3,2-ef] [2] benzazepin- 6-ol, is classified as a phenanthrene alkaloid, chemically similar to codeine—a sleep-inducing drug derived from

morphine. Originally isolated from the snowdrop plant, *Galanthus nivalis*, Galantamine's pharmacological distinctiveness comes from its dual mode of action. It works as a reversible, competitive inhibitor of AChE and binds to both the choline binding site and acetyl binding site on the enzyme (Stepankova & Komers, 2008). In addition, it functions as an allosteric modulator of nicotinic acetylcholine receptors in the brain, enhancing the release of acetylcholine from presynaptic terminals. Similar to donepezil, galantamine demonstrates over ten-fold selectivity for AChE over BChE, increasing its efficiency and specificity compared to non-selective drugs (Stepankova & Komers, 2008).

**Chemical Structure and Background of Rivastigmine**

Rivastigmine's IUPAC name for rivastigmine is 3-[(1S)-1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate, and belongs to the miotine derivative family, a group of compounds known for their cholinesterase-inhibiting effects (Drugbank, 2005a). It inhibits AChE in both laboratory settings and living organisms and is most effective at reducing the enzyme in particularly at the hippocampus and cortex. Rivastigmine is classified as a long-acting, pseudo-irreversible, non-competitive cholinesterase inhibitor, meaning it binds strongly to the enzyme and for a prolonged time. Its carbamate structure, as seen in Figure 1, allows it to form a temporary chemical bond with the esteratic site of AChE (Colovic et al., 2013). Unlike donepezil and galantamine, rivastigmine acts on both AChE and BChE enzymes, which may make it more useful in more advanced stages of AD. It primarily acts within the central nervous system, helping limit unwanted effects in other parts of the body; these are further mitigated in the oral medication

Zunveyl, and its effectiveness and tolerability in individuals surpasses reviews from patients on donepezil and galantamine.

## Conclusion

This review provided an overview of the three FDA-approved cholinesterase inhibitors available for use in Alzheimer's Disease treatments. While cholinesterase inhibitors do not cure AD, they provide significant symptomatic relief by enhancing chemical activity in the brain to improve memory and other cognitive functions. However, they come with a range of physical and emotional side effects that need to be carefully managed. While donepezil and galantamine, two acetylcholinesterase inhibitors, can improve cognitive functions, they can also cause emotional instability and unbalanced physical side effects. Rivastigmine, which inhibits both acetylcholinesterase and butyrylcholinesterase, offers an alternative with its patch that increases the durability of action in the body but comes with risks for emotional disturbances. Ongoing research and careful patient monitoring are essential to further the development of Alzheimer's Disease treatments while curtailing adverse effects to provide a balanced approach to treating AD.

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