



Donepezil Beyond Alzheimer's Disease? A Narrative Review of Therapeutic Potentials of Donepezil in Different Diseases

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Abstract

Donepezil hydrochloride is an acetylcholine esterase inhibitor studied and approved to treat Alzheimer's disease (AD). However, this drug can have positive therapeutic potential in treating different conditions, including various neurodegenerative disorders such as other types of dementia, multiple sclerosis, Parkinson's disease, psychiatric and mood disorders, and even infectious diseases. Hence, this study reviewed the therapeutic potential of this drug in treating Alzheimer's and other diseases by reviewing the articles from databases including Web of Science, Scopus, PubMed, Cochrane, and Science Direct. It was shown that donepezil could affect the pathophysiology of these diseases via mechanisms such as increasing the concentration of acetylcholine, modulating local and systemic inflammatory processes, affecting acetylcholine receptors like nicotinic and muscarinic receptors, and activating various cellular signaling via receptors like sigma-1 receptors. Despite many therapeutic potentials, this drug has not yet been approved for treating non-Alzheimer's diseases, and more comprehensive studies are needed.

Keywords: Donepezil, Alzheimer's Disease, Parkinson's Disease, Vascular Dementia, Traumatic Brain Injury, Multiple Sclerosis, Mental Disorder, Sleep Disorder, Infectious Disease

1. Context

Donepezil hydrochloride with the formula of $C_{24}H_{30}ClNO_3$ and molecular weight of 416 Dalton is a second-generation acetylcholine esterase inhibitor (AChEI) that was first produced by the Eisai Company (1-3). This drug consists of a benzylpiperidine part bound to dimethoxy indanone via the methylene group (4). Donepezil binds selectively, reversibly, and non-competitively to the peripheral anionic site of acetylcholine esterase (AChE) (2, 5). It has a greater tendency to inhibit AChE than butyrylcholine esterase (BuChE), among other AChEIs, and some studies represented the clinical significance of this difference, especially in Alzheimer's disease (AD) (5, 6).

Donepezil has a relatively slow gastrointestinal absorption and takes 3 to 5 hours to reach peak plasma concentrations. Furthermore, the absorption of this drug does not interfere with food and, at the same time, has good bioavailability. Donepezil binds relatively well to serum proteins like albumin and is excreted more readily in the urine. This drug also has hepatic metabolism. Cytochrome

P450 CYP2D6, CYP3A4, CYP3A5, and CYP2C9 are the enzymes involved in the metabolism of donepezil. However, CYP2D6 and CYP3A4 are thought to have the primary role in the metabolism of this drug in the liver (5, 7). On the other hand, this medicine has a half-life of 70 hours, reducing the number of tablets required during the day and improving patient compliance (5, 8). The steady-state concentration (C_{ss}) of this drug increases with dose so that it is about 30 ng/mL at the dose of 5 mg/day and about 60 ng/mL at 10 mg/day. However, the concentration of donepezil in the cerebrospinal fluid (CSF) is much lower than in plasma but is still dose-dependent (5, 8).

It also appears that donepezil has low drug interactions and good tolerability in side effects, especially at lower doses (5, 8). Common adverse effects of this drug include cholinergic side effects, such as nausea, vomiting, diarrhea, insomnia, anorexia, fatigue, muscle cramps, increased gastrointestinal secretions, and even effects on the vagus nerve and cardiac arrhythmias, which are dose-dependent (5, 9, 10).

Although donepezil was approved by the US Food and

Drug Administration (FDA) to treat various stages of AD, and most studies have examined the effect of this drug on AD (5, 10), donepezil has some therapeutic potential in other dementia and non-dementia diseases such as improving movement and dementia in Parkinson's disease and positively affecting sleep disorders, psychiatric diseases, and even infectious diseases (11-14). Therefore, we aimed to review these effects in the present study, in addition to the role of this drug in treating AD. Hence, we surveyed these therapeutic potentials into two general topics: "donepezil and dementia" and "donepezil and non-dementia diseases."

2. Evidence Acquisition

This study aimed to review the studies on different therapeutic potentials of donepezil. The search keywords included donepezil hydrochloride, AD, memory impairment, dementia, cognitive impairment, vascular dementia, Parkinson's dementia, traumatic brain injury dementia, multiple sclerosis, neurologic disease, neuropsychiatry disease, Parkinson's disease, depression, mood disorders, antidepressant, schizophrenia, autism spectrum disorder, sleep disorders, immune system, infections, and COVID-19.

We reviewed all studies and articles in English in the national and international journals published between 2008 and 2022 in valid databases such as web of science, Google scholar, PubMed, Scopus, Cochrane, and science direct. Then, clinical trials, preclinical studies, case reports, cohorts, narrative reviews, systematic reviews, and meta-analyses related to the aims of the present study were included. Also, keywords were chosen based on the frequency and importance of studies in the initial search.

2.1. Donepezil and Dementia

2.1.1. Alzheimer's Disease and Donepezil

Alzheimer's is a progressive neurodegenerative disease affecting patients' cognitive and executive skills. It is one of the most frequent kinds of dementia and has the potential to cause disability and perhaps death. An estimated 57 million people worldwide suffered in 2019, which is expected to multiply by 2050. Therefore, this disease is a challenge to health care systems regarding cost burden and various consequences for individuals, families, and care systems (10, 15, 16). Therefore, donepezil is one of the drugs approved by the FDA to treat this disease in mild, moderate, and severe states, used both as monotherapy and in combination therapy with other drugs such as memantine. In addition to improving the symptoms

of AD, this medicine has shown to be reasonably successful in slowing down the development of the disease, particularly in the early stages by the early prescription of the drug. It is, nevertheless, a reasonably safe medicine with a few adverse effects that are well tolerated (5, 10, 17, 18). Based on the evidence, it seems that different mechanisms, such as amyloid-beta ($A\beta$) plaque accumulation, tau pathology, glutamate excitotoxicity, oxidative stress, neuroinflammation, and vascular changes are involved in the pathophysiology of AD, which together lead to the neuronal and synaptic loss and atrophy in some areas such as the hippocampus and prefrontal cortex, responsible for cognitive, behavioral, and executive processes. As a result, studies show that donepezil may influence these pathways via various mechanisms, altering disease symptoms and progression (15, 18-20).

As known, one of the most important pathologies of AD is the accumulation of $A\beta$ in the critical areas of the brain, such as the hippocampus. According to various pre-clinical and clinical studies, donepezil can reduce the accumulation and destructive effects of $A\beta$ in the brain via different mechanisms, such as reducing the conversion of amyloid precursor protein (APP) to $A\beta$, increasing cholinergic pathways and synapses in the brain, followed by a decreased beta-secretase activity that is involved in $A\beta$ production, and increasing the ratio of acetylcholinesterase read-through isoform (AChE-R), which has a protective effect on the neurons, to synaptic isoform (AChE-S), whose high expression leads to neuronal damage (Figure 1) (15, 17, 18).

Studies have shown that $A\beta$ could activate microglial cells via the nuclear factor-kappa B (NF- κ B) and mitogen-activated protein kinase (MAPK) signaling pathways, which, in turn, activate inflammatory pathways and secrete neurotoxins and cytokines, consequently leading to cell apoptosis and neurodegeneration processes in the CNS, especially in the hippocampal formation. Donepezil can inhibit the NF- κ B and MAPK signaling pathways, as well as the activation of microglia cells. It can also reduce the production of cytokines and inflammatory factors, such as tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), IL-6, nitric oxide (NO), and prostaglandin E2 (PGE₂) in a dose-dependent way. It can also inhibit the expression of proinflammatory factor genes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2).

On the other hand, donepezil may suppress the release of other neurotoxic factors from microglia, as well as the processes of microgliosis and astrogliosis, which worsen inflammation, and have protective effects on neurons and memory via these pathways (15, 18-20). Besides, one of the cell-destructive mechanisms in AD is glutamate toxic-

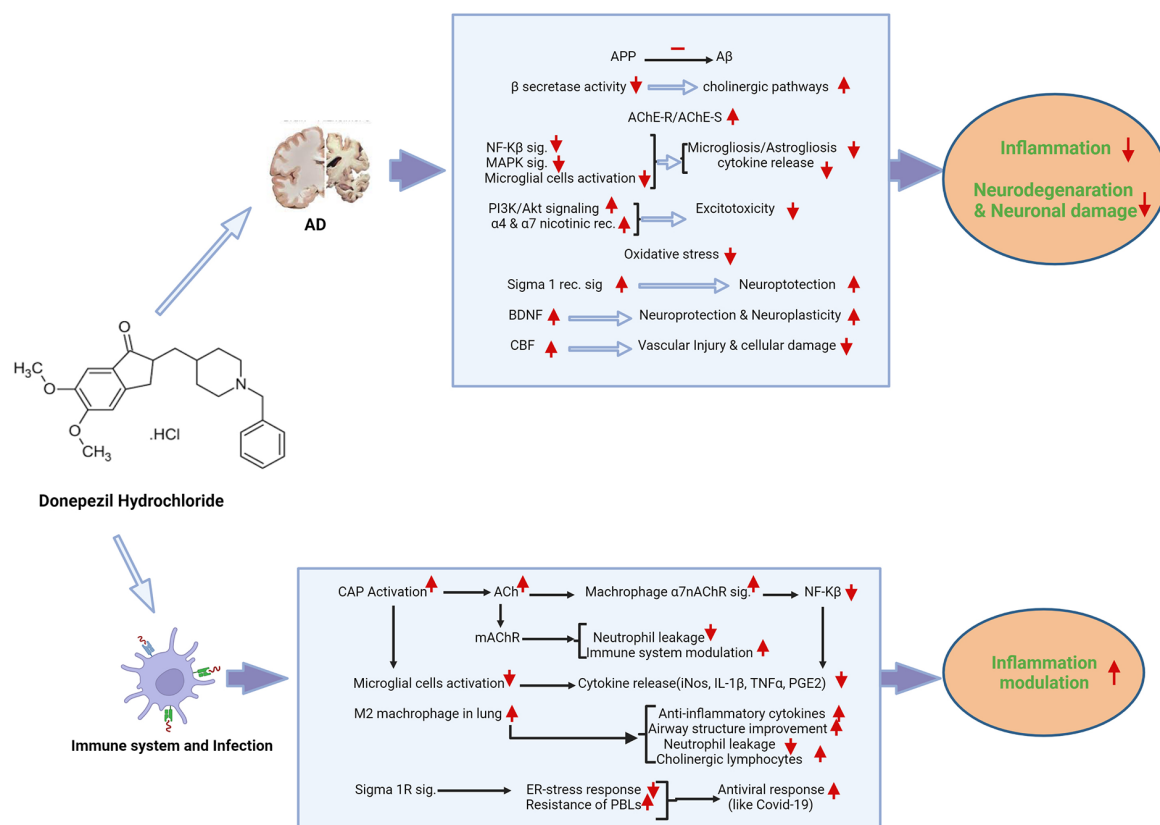


Figure 1. Summary of donepezil effects on Alzheimer's disease and immune system. Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; A β , amyloid-beta; AChE-R, acetylcholinesterase read-through isoform; AChE-S, acetylcholinesterase synaptic isoform; NF- κ B, nuclear factor-kappa B; MAPK, mitogen-activated protein kinase; Sig., signaling; PI3K/Akt pathway, phosphatidylinositol 3-kinases/protein kinase B pathway; Rec, receptor; BDNF, brain-derived neurotrophic factor; CBF, cerebral blood flow; CAP, cholinergic anti-inflammatory pathway; Ach, acetylcholine; α 7nAChR, alpha 7 nicotinic acetylcholine receptor; mAChR, muscarinic acetylcholine receptor; iNOS, inducible nitric oxide synthase; IL-1 β , interleukin-1 β ; TNF α , tumor necrosis factor alpha; PGE2, prostaglandin E2; Sigma 1R sig., sigma-1 receptor signaling; ER-stress, endoplasmic reticulum stress; PBLs, peripheral blood leukocytes.

ity and excitotoxicity process, which enhances the harmful effects of A β accumulation and tau pathology. Therefore, donepezil can play a protective role against these destructive processes by activating the Phosphatidylinositol 3-kinases/protein kinase B (PI3K-Akt) pathway and increasing α 4 and α 7 nicotinic receptors, which reduce the activation of N-methyl-D-aspartate (NMDA) receptors and apoptosis following calcium accumulation in the neurons (15, 18, 21, 22). Donepezil also protects the hippocampus and cerebral cortex from oxidative stress by inhibiting glutathione reduction and reducing inflammatory processes (15, 18, 23, 24). Donepezil may also affect the pathophysiology of AD via binding to the sigma-1 receptor, which is found in many areas of the brain, such as the CA1 region of the hippocampus, thalamus, cortex, cerebellum, and spinal cord. It is found on the membrane of the cell's endoplasmic reticulum. Moreover, it has a neuromodulatory, neuroprotective, neuroplasticity, and anti-apoptotic role.

Therefore, donepezil, with the high binding capacity to this receptor, can play a protective role against pathologies and destructive mechanisms of AD, such as beta-amyloid accumulation and tau pathology (Figure 1) (15, 18, 25, 26).

Increased brain-derived neurotrophic factor (BDNF), which has a neuroplasticity impact on the cortex and hippocampus, is another protective mechanism of donepezil in AD. According to studies, donepezil can reduce ischemia-induced cellular damage and maintain the function of neurons in different areas of the brain, especially the medial temporal lobe (hippocampus and parahippocampus), cingulate gyrus, and prefrontal cortex, by regulating blood flow in cerebral arteries and reducing amyloid accumulation-induced microvascular damage (Figure 1) (15, 18).

Bond et al. concluded that donepezil was more cost-effective than other AChEIs, memantine, placebo, and high-quality supportive care in AD with mild to moder-

ate severity in a systematic review and economic analysis (27). Furthermore, in a meta-analysis by Li et al., which analyzed the clinical trials of the efficacy and safety of common drugs used to treat AD, such as donepezil, galantamine, rivastigmine, and memantine, it was found that donepezil had significant efficacy in stabilizing or slowing down the reduction in cognitive and executive functions, behavioral indices, and global changes in AD patients with mild, moderate, and severe severity; it was also relatively safe in terms of tolerability and side effects (28). In another study, Kim et al. examined the effect of donepezil on the pathophysiology of AD in an animal model. They found that donepezil, both in vitro and in vivo, had a substantial modifying influence on disease-causing and exacerbating pathways, delaying disease progression and enhancing memory (19). Zhang and Gordon reviewed the effects of donepezil on treating AD in Chinese patients and showed that it was highly effective in treating mild to moderate AD and was probably influential in treating the severe type. It also reduced AD biomarkers, such as $A\beta$, tau protein, and hippocampal atrophy (29). However, according to a review study by Adlimoghaddam et al., donepezil can be effective in treating AD at different stages, although this effect is little (10). Furthermore, some studies have shown that donepezil has no significant effect on mild cognitive impairment and amnesia and could not prevent the progression of mild cognitive impairment to AD (30). It should be noted that based on various studies, the effectiveness of donepezil in AD treatment increases with increasing doses (5, 10, 17, 27). However, side effects are also more common at higher doses (Table 1) (10, 31).

According to studies and guidelines in treating mild to moderate AD, donepezil 5 mg per day is typically used for four to six weeks, after which it can be increased to 10 mg daily. The dose can be increased to 23 mg daily for patients with moderate to severe AD treated with donepezil 10 mg daily after at least three months (10, 31).

2.1.2. Parkinson's Dementia and Donepezil

Although Parkinson's disease (PD) is often considered a neurodegenerative motor disorder, it was shown to have a range of cognitive and memory impairments (32, 45). It seems that this cognitive disorder has a relatively high prevalence. Some studies have shown a 40% prevalence of mild cognitive disorder in patients in the early stages, which can increase the risk of dementia in the higher stages of the disease. Moreover, some studies indicated an 80% prevalence of dementia among patients with advanced stages of the disease. This condition is critical because of its negative consequences for patients and their families (45). Various types of cognitive impairments in Parkinson's disease may be manifested; however, it can

be categorized into two categories: (1) Parkinson's disease with mild cognitive impairment (PD-MCI) that mainly affects the executive areas of the brain and working memory, such as frontal lobes and frontal-striatal pathways and is divided into two sub-categories: Single domain PD-MCI, which one cognitive domain impairment is detected without other cognitive domains damage in two abnormal cognitive test results, and multidomain PD-MCI, which more than one cognitive domain damage is detected in at least one abnormal test., and (2) Parkinson's disease dementia (PDD), a destructive cognitive impairment that can affect broad domains of cognition such as semantic verbal fluency, attention, and visual-spatial strength, originated from damage to the temporal lobe and other areas (45-47).

Various mechanisms have been proposed for the pathophysiology of various manifestations of cognitive impairment due to Parkinson's disease, such as the prominent role of dopaminergic and noradrenergic networks and receptors in areas of the brain related to executive function, including frontostriatal and mesocortical pathways, the prominent role of cholinergic neural networks in the process of attention, memory, executive function, and in areas such as the medial temporal lobe, especially the hippocampus, frontoparietal, occipital, and nucleus basalis of meynert (NBM), and the role of the noradrenergic system in many processes like concentration and executive function, such as the locus coeruleus and the frontoparietal pathway (11, 45, 48). Because of the importance of cholinergic neural pathways in the pathophysiology of PD-MCI and PDD, as well as the destruction of these pathways and innervations by mechanisms like alpha-synuclein, $A\beta$, and tau protein accumulation, AChEIs like donepezil and rivastigmine have been considered in many studies (Figure 2). Moreover, the results indicated the appropriate effectiveness of these drugs in various manifestations of cognitive impairment and dementia due to PD and improvement of patients' general cognition and executive function; in some studies, these effects were even more significant than the effects of these drugs in AD patients (13, 45, 48).

In a placebo-controlled randomized, double-blind clinical trial study of donepezil efficacy and safety in PDD patients, performed by Dubois et al. with a relatively high sample size (550 participants) and doses of 5 and 10 mg donepezil daily, donepezil could be relatively effective with minimal side effects and well tolerability, improving cognition, general condition, and executive function of PDD patients (49). Wang et al. performed a systematic review and meta-analysis of clinical trials on the effectiveness and harmlessness of cholinesterase inhibitors and memantine in PDD, PD-MCI, and Lewy bodies dementia (LBD) before May 2013. This research revealed that donepezil could

Table 1. Summary of Studies Regarding the Various Therapeutic Potentials of Donepezil

Type of Disease	Author	Type of Study	Dosage and Method of Administration	Number of Participants	Outcomes Summary
Donepezil and Non-Alzheimer's Dementia					
Parkinson's dementia	Wang et al. (32)	Systematic review and meta-analysis	5 and 10 mg/daily, oral	Five trials examining DPZ	DPZ improved patients' daily functioning and cognitive symptoms. It was safe and could be helpful for MCI-PD, PDD, and LBD.
Vascular dementia	Kim et al. (33)	Meta-analysis	5 and 10 mg/daily, oral	Five trials examined DPZ	AChEIs, including DPZ, significantly improved memory scale scores and maintained this improvement within 24 weeks through a stable pattern. They were well-tolerated.
Vascular dementia	Battle et al. (34)	Meta-analysis and network meta-analysis	5 and 10 mg/daily, oral	Three trials studying DPZ (2,193 participants)	According to the meta-analysis, DPZ 5 and 10 mg had a negligible effect on cognitive improvement, although the side effects of the 10 mg dose were higher; However, according to the network meta-analysis, all AChEIs were more effective and safer than placebo.
Traumatic brain injury dementia	Wheaton et al. (35)	Meta-analysis	5 - 10 mg/day, oral	Six studies (DPZ/DPZ + physostigmine + lecithin)	Improvement of memory and attention impairment in the post-acute phase of TBI
Traumatic brain injury dementia	Campbell et al. (36)	Retrospective, longitudinal analysis	5 - 10 mg/day, oral	129 patients (55 patients in the DPZ group)	There was no significant difference between the two groups regarding cognitive factors such as processing speed, attention, and memory.
Donepezil and Non-dementia Diseases					
Parkinson's disease	Chung et al. (37)	Cross-over RCT	5 - 10 mg/day, oral	23 patients with PD with falls or near falls > 2 times per week	The number of falls per day in the DPZ group was almost half that of the placebo group.
Parkinson's disease	Chen et al. (12)	Meta-analysis	5 and 10 mg/daily, oral	Three studies examining DPZ	AChEIs could not significantly improve gait and imbalance, although these drugs appeared to be relatively effective in regulating steps during a single activity.
Mood disorders	Reynolds et al. (38)	Clinical trial	5 - 10 mg/day, oral	130 patients with normal cognition or MCI	Improvement of executive function and memory; More recurrence of depression than the placebo group
Mood disorders	Fitzgerald et al. (39)	Animal study	0.02 - 0.2 mg/kg, and 2 mg/kg, intraperitoneally injected	160 mice	The antidepressant-like effect at lower doses and depressant-like effect at higher doses
Mood disorders	Hosseini et al. (40)	Clinical trial	5 mg/day, oral	73 patients aged 20 - 50 years old (37 patients in the DPZ group and the rest in the placebo group)	DPZ significantly improved cognitive impairment caused by SSRIs
Autism spectrum disorders	Gabis et al. (41)	Clinical trial	2.5 - 5 mg/day, and DPZ 5 mg/day + Choline 350 mg/day for four weeks, oral	60 autistic children and adolescents (5 - 16 years old)	Significant safety and efficacy in young children (younger than 10 years old); Less effective in adolescents with some significant side effects like increased irritability.
Autism spectrum disorders	Rossignol and Frye (42)	Systematic review	2.5 - 30 mg/day, oral	Seven studies	Five studies showed improvement of many ASD symptoms (four of five case series and one of two RCTs).
Immune system and infectious disease	Abe et al. (43)	Retrospective cohort study	-	25,602 hospitalized elderlies with pneumonia (578 patients taking DPZ for dementia)	DPZ acted as an independent factor in reducing hospitalized pneumonia patients' mortality.
Immune system and infectious disease	Sochocka et al. (44)	Experimental	5 - 100 µg/mL, in vitro	PBLs from 30 blood samples (15 with resistant leukocytes to VSV and 15 with sensitive leukocytes) treated with DPZ or EGB-761	10 - 50 µg/mL DPZ increased resistance of human leukocytes and reduced activation of NF-κB.

Abbreviations: AChEI, acetylcholinesterase inhibitor; DPZ, donepezil hydrochloride; EGB 761, Ginkgo biloba extract *EGB 761*; LBD, lewy body dementia; MCI, mild cognitive impairment; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PBLs, peripheral blood leukocytes; PD, Parkinson's disease; PDD, Parkinson's disease dementia; RCT, randomized controlled trial; SSRIs, selective serotonin reuptake inhibitors; TBI, traumatic brain injury; VSV, vesicular stomatitis virus.

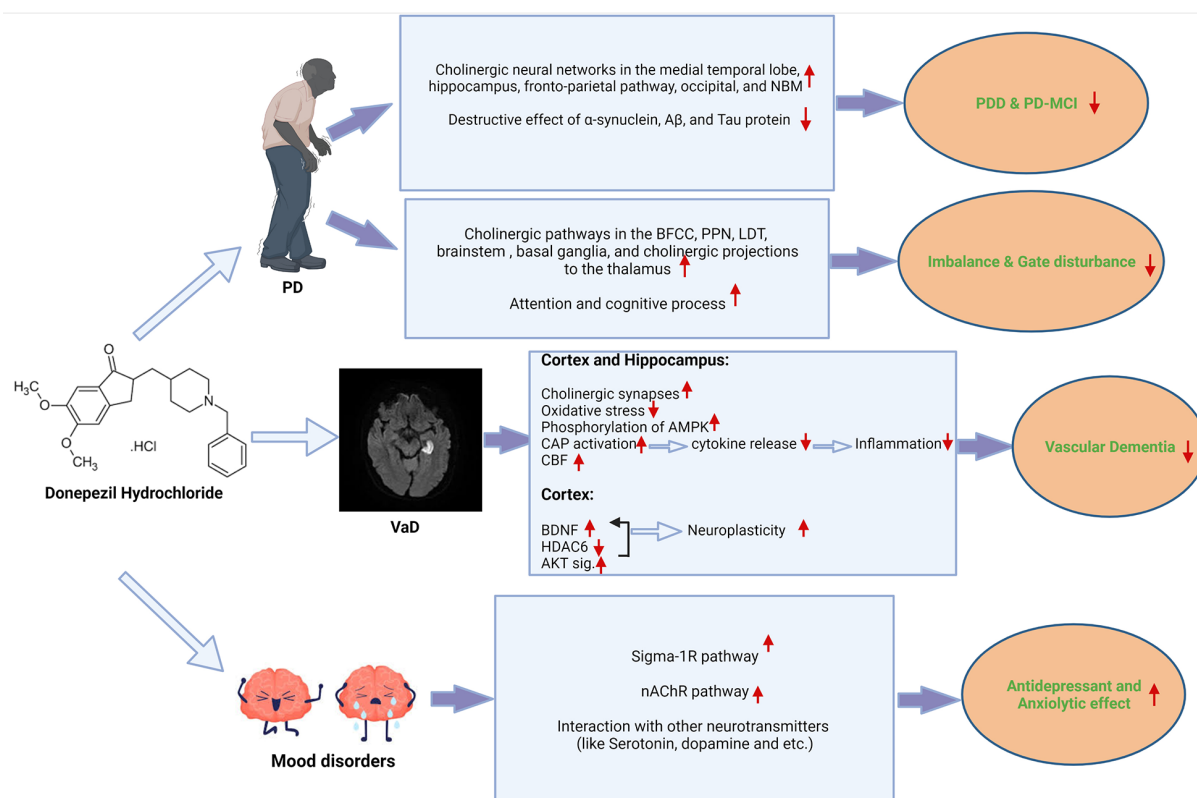


Figure 2. Summary of donepezil effects on Parkinson's disease dementia and motor impairments, vascular dementia, and mood disorders. Abbreviations: PD, Parkinson's disease; NBM, nucleus Basalis of Meynert; A β , amyloid-beta; PDD, Parkinson's disease dementia; PD-MCI, Parkinson's disease with mild cognitive impairment; BFCC, basal forebrain cholinergic complex; PPN, pedunculo-pontine nucleus; LDT, latero-dorsal tegmental nucleus; VaD, vascular dementia; AMPK, AMP-activated protein kinase; CAP, cholinergic anti-inflammatory pathway; CBF, cerebral blood flow; BDNF, brain-derived neurotrophic factor; HDAC6, histone deacetylase 6; AKT, protein kinase B; Sigma-1R, sigma-1 receptor; nAChR, nicotinic acetylcholine receptor.

improve patients' daily functioning, cognitive symptoms, and overall effectiveness in clinicians' global impression of change. In terms of adverse effects, it is a safe medicine and may benefit PD-MCI, PDD, and LBD (32) (Table 1). Despite all the above results, due to different findings about the efficacy of this drug in Parkinson's dementia, donepezil has not been approved yet and is used off-label, and only rivastigmine has been approved among AChEIs (11, 13).

2.1.3. Vascular Dementia

Vascular cognitive impairment (VCI) is another cognitive disorder that ranges from mild to severe (34, 50). This entity occurs due to vascular impairment, especially in brain vessels (34, 51). Vascular dementia is one of the most common types of VCI and the second most common dementia after AD. Memory loss, executive dysfunction like decision-making and problem-solving, speech impairment and aphasia, visual impairment, behavioral and mood disorders like anxiety and depression, and even gait

and balance impairments are common signs and symptoms of this dementia (34, 51, 52). Although no drug has been approved for treating this dementia, various studies were performed on cholinesterase inhibitors, including donepezil, which has been approved for treating AD (33, 34, 52, 53). Kim et al. meta-analyzed seven studies that investigated the effect of AChEIs on memory impairment after CVA and vascular dementia, finding that these drugs, including donepezil, significantly improved memory scales scores, such as mini-mental state examination (MMSE) and AD assessment scale-cognitive subscale (ADAS-cog) scores, and also maintained memory improvement within 24 weeks through a stable pattern compared to the placebo. These medications are also well tolerated and generally safe regarding adverse effects (33). Another meta-analysis of eight clinical studies by Battle et al. found that donepezil 5 mg might enhance cognition in individuals with vascular dementia or other cognitive vascular impairments, albeit the result was not clinically significant. It

was also found that donepezil 10 mg daily was probably a little more than 5 mg effective in cognitive impairment but still not clinically significant. However, the side effects of donepezil 10 mg appeared to be slightly higher than those of 5 mg compared to the placebo. On the other hand, according to a network meta-analysis, all AChEIs were in a higher position than the placebo in terms of efficacy and a lower position in terms of side effects. It was also found that donepezil 10 mg/day ranked first in terms of benefits and third in terms of side effects among other AChEIs analyzed in this meta-analysis (including donepezil 5 mg/day, rivastigmine 3 to 12 mg/day, and galantamine 16 to 24 mg/day) (Table 1) (34).

According to studies, donepezil affects the pathophysiology of vascular dementia via various mechanisms. In a study by Jian et al., which examined the effect of donepezil on vascular dementia in rats experimentally subjected to bilateral obstruction of the common carotid artery, this drug could increase neuronal activity and prevent neurodegeneration due to vascular impairment through various mechanisms, such as increasing BDNF gene expression (an essential factor in the neuroplasticity and neuronal activity) directly and indirectly (by reducing nuclear translocation of histone deacetylase 6 (HDAC6), which is a regulatory factor in BDNF gene expression) in the cortex (regarding the critical role of the cortex in long-term memory), returning the density of dendritic synapses to near normal in the hippocampus and cortex, reducing oxidative stress due to free radicals, activating the AMP-activated protein kinase (AMPK) pathway in the hippocampus and cortex, and activating the protein kinase B (AKT) pathway in the cortex (52). Another study by Sharma and Singh which examined the effects of telmisartan and donepezil on vascular dementia due to hypertension induced by deoxycorticosterone acetate-salt in mice, achieved similar results and found that donepezil via mechanisms, such as activating the cholinergic anti-inflammatory pathway to inhibit the secretion of proinflammatory factors and cytokines, reducing oxidative stress, and inhibiting the brain cholinesterase, improves vascular endothelial task, regulates cerebral blood flow, and overall improves vascular dementia (Figure 2) (Table 1) (51). Other studies also pointed to these mechanisms (33, 54). Despite this evidence, this drug has not yet been approved for the treatment of vascular dementia (55).

2.1.4. Traumatic Brain Injury Dementia

Traumatic brain injury (TBI) is one of the leading factors of mortality and morbidity in many countries, especially developing countries (56, 57). A strike or pressure can cause this injury to the skull following a fall and accident or direct trauma to the head during sports and

fights such as boxing and football. This trauma can cause various symptoms, such as Parkinson's-like symptoms, including tremors, gait and balance disorders, behavioral and psychiatric diseases, and sleep disorders. Concerning the specific anatomy of the brain and skull, it seems that this damage can lead to diffuse axonal injury, progressive neurodegeneration, and atrophy in different areas of the brain, especially vulnerable areas such as the hippocampus, amygdala, and frontal cortex, which have essential roles in cognitive processes and executive functions; thus, such damages can cause cognitive problems and dementia even years after the injury (56-59). As a result, research has sought to develop new treatments to ameliorate the symptoms and complications of this injury, but the FDA has yet approved no treatment; therefore, the pharmaceuticals are administered off-label (58-60). Studies showed that the pathology, brain changes, and cognitive impairment patterns following TBI are similar in aspects to Alzheimer's dementia. For example, TBI, like Alzheimer's, can affect short-term and long-term memory or cause behavioral and mood disorders. Aggregation of beta-amyloid plaques and neurofibrillary tangles, followed by neurodegeneration and atrophy in areas such as the medial temporal lobe and hippocampus, parahippocampal gyrus, thalamus, hypothalamus, and amygdala, are seen in both AD and TBI. However, this pattern of pathology differs from AD in some aspects. In addition, changes and destruction of cholinergic nerve pathways have been observed in TBI, similar to AD. Therefore, due to the similarities in the physiopathology and symptoms of TBI and AD, one of the drugs considered in the studies and prescribed off-label is AChEIs, especially donepezil (56-61). Yu et al. used transgenic mice to examine the effect and mechanism of donepezil for improving post-TBI memory impairment and found that it was effective in improving learning and spatial memory after injury and neurogenesis. However, it appeared that the drug's effectiveness was greater in memory impairment through mechanisms other than neurogenesis after injury (61). Furthermore, a meta-analysis by Wheaton et al. analyzed five studies that examined the effectiveness of donepezil alone and one study that examined the effectiveness of donepezil in combination with physostigmine and lecithin for improving cognitive symptoms after the acute stage of brain injury (four weeks after injury) at different disease severities, concluding that donepezil could improve attention and memory at different TBI severities (35).

Moreover, in a meta-analysis by Bengtsson and Godbolt which analyzed clinical trials examining the effect of AChEIs on TBI-induced cognitive impairment beginning at least 12 months after injury, it was found that donepezil at a dose of 10 mg had a significant effect on improving vi-

sual memory and learning. However, this effect was not observed at a dose of 5 mg (56). Campbell et al. made a retrospective comparison of the effect of donepezil (starting 5 mg daily and increasing to 10 mg daily seven to 10 days after starting treatment) with rehabilitation therapy on cognitive factors during the acute recovery phase of moderate to severe TBI among 129 patients (55 in the donepezil group and 74 in the rehabilitation group). They found that the two groups had no significant differences (Table 1) (36). However, many studies recommend a dose of 5 - 10 mg to treat TBI-induced cognitive impairment (58-60).

2.1.5. Multiple Sclerosis Cognitive Dysfunction

Multiple sclerosis is a demyelinating disease that can cause disability, especially in young people (62). One of the relatively common problems of this disease is cognitive impairment, which affects various areas of cognition such as working memory, executive function, episodic memory, and attention, and reduces the quality of life and even results in depression in the patients. Therefore, various studies have investigated the pathophysiology of this cognitive disorder and its treatment (62, 63). Evidence suggests that a defect in the hippocampal cholinergic system is one of the underlying mechanisms, similar to AD pathophysiology (64). Hence, donepezil is one of the drugs considered in studies (62, 63, 65). According to two studies by Shahpouri et al., donepezil could improve cognition, executive function, depression, and quality of life (62, 65). However, according to a study by O'Carroll et al., this drug did not significantly improve cognition (63). Therefore, more studies are needed to make a definite decision.

2.1.6. Schizophrenia Cognitive Impairment

Schizophrenia is a psychiatric disease with diverse symptoms such as hallucination and delusion. Impairments in different domains of cognition such as working memory, attention, executive function, and language skills are other important and influential symptoms in the daily life of people with the disorder. Therefore, various studies have tried to find a treatment for this cognitive impairment (66, 67). According to some radiological, autopsy, molecular, and histological evidence showing impairment in the cholinergic system and the nicotinic and muscarinic receptors in many cognitive areas such as the hippocampus formation, cortex, and basal ganglia, the effectiveness of acetylcholinesterase inhibitors, especially donepezil, has been considered in studies (67, 68). However, studies have shown mixed results. For example, Zhu et al. examined the effectiveness of donepezil 5 mg for 12 weeks in patients with chronic schizophrenia treated with antipsychotic drugs. The results showed that this drug could significantly improve cognition domains such

as working memory and visual learning (66). However, another study by Hsu et al. found that donepezil could not significantly improve cognitive impairments (69). Therefore, further research is needed for the exact conclusion.

2.2. Donepezil and Non-dementia Diseases

2.2.1. Parkinson's Disease

According to studies, in addition to the applications of donepezil for different types of dementia, it can also play a role in some other non-dementia neurological diseases. Among them is the use of donepezil to improve balance and gait disorders caused by Parkinson's disease (12, 70).

Parkinson's is a neurodegenerative disease characterized by various symptoms, including tremors, imbalance, and gait disturbance. Consequently, these symptoms may reduce a person's quality of life, induce frequent falls and fear of falling, and even endanger their lives. Therefore, various studies were conducted to find the mechanisms of this disease and its treatment. According to studies, dopaminergic drugs, such as levodopa, which play a pivotal role in treating Parkinson's disease, do not appear to be effective in improving balance and gait disorders. Therefore, studies have proposed various theories for the physiopathology of this disorder, including the role of cholinergic neurons and branches in the structures and centers involved in the movement, such as the basal forebrain cholinergic complex (BFCC), pedunculopontine (PPN), and laterodorsal tegmental nuclei, cholinergic pathways in the brainstem and basal ganglia, and cholinergic projections to the thalamus. The role of cognitive processes such as attention, memory, and executive function in gait and keeping balance is also mentioned. Therefore, as mentioned in the section "Parkinson's dementia," the cholinergic system plays a fundamental role in cognitive processes (Figure 2) (12, 37, 70-74).

However, studies have shown diverse outcomes. A cross-over clinical study conducted by Chung et al. in 2010 examined the effectiveness of donepezil in preventing falls in 23 individuals with Parkinson's disease with a history of falls or near falls more than two times per week over 15 weeks and found that the number of falls per day in the donepezil group was approximately half that of the placebo group (37). Moreover, Stuart et al. conducted a cross-over clinical trial to evaluate the efficacy of a combination of cholinergic drugs (donepezil 5 mg) and dopaminergic drugs (levodopa) in the treatment of gait problems among 19 patients with Parkinson's disease over 50 years of age and treated with levodopa, with a score of 2 to 4 on the Hoehn and Yahr scale. They found that levodopa reduced the activity of the prefrontal cortex, which plays a vital role in executive function. Nevertheless, it did not happen in the combination of donepezil and levodopa.

Also, the accuracy of performing two tasks simultaneously while using levodopa and donepezil increased compared to using levodopa alone. During the simultaneous use of donepezil and levodopa, gait function and its components, such as gait speed and stride length, were also improved compared to levodopa and placebo during single and binary activity (70). However, the meta-analysis by Chen et al. found that AChEIs did not substantially enhance gait and balance, despite that these medications appeared to be relatively effective in regulating steps during single activities (12). Moreover, the study by Mancini et al. (74) on 45 patients with Parkinson's disease, with relatively similar conditions to the study by Stuart et al. (70), showed that donepezil had no significant effect on improving motor and balance components in Parkinson's patients (Table 1) (74). In general, the findings tend to vary depending on the methods and measurement scales. These studies had a small sample size as well. As a result, larger sample sizes and more precise and sensitive scales are required for more accurate results.

2.2.2. Sleep Disorders

Donepezil may have a role in improving sleep disorders in healthy and Alzheimer's patients, Lewy dementia, autism spectrum disorder, obstructive sleep apnea, and mood disorders such as depression (13, 75-78). According to various studies, due to its impact on increasing the acetylcholine concentration in the brain and the critical role of this neurotransmitter in sleep processes, donepezil can increase the percentage of rapid eye movement (REM) sleep and regulate REM latency in individuals (13, 75, 79).

2.2.3. Mood Disorders

Donepezil and AChEIs have shown mood-modifying properties in animal and clinical trials. However, some research has refuted this efficacy, and the findings of specific studies have shown that these medicines cause depression, mania, or even exacerbation of the underlying condition (13, 80). In an animal study by Papp et al., using 96 rats in both stress and control groups, the anxiolytic, antidepressant, and cognitive-improving effects of donepezil (0.3 mg/kg intraperitoneally), rivastigmine, imipramine, and memantine were investigated. The results indicated the efficacy of donepezil in improving the symptoms of anxiety, depression, and cognition impairment (81). Moreover, in a case report by Lim et al., the antidepressant effect of donepezil at a dose of 5 mg as adjunctive therapy was noticed in a 62-year-old woman with a history of depression without any cognitive problems whose depression was resistant to routine depression treatments and even next-line drugs (82). However, as previously stated, some studies have shown inconsistent evidence regarding donepezil's

efficacy in treating depression (80, 83). Reynolds et al., for example, in a clinical trial study, found that donepezil was ineffective in treating depression in 130 older adults with depression and mild cognitive impairment (38). There is an important theory about the antidepressant effects of donepezil: this drug follows the Janus-faced (u-shaped) dose-response curve. In other words, this drug shows antidepressant effects at low and usual doses and depression-like effects at higher doses (13, 39, 80). Various studies confirm this theory. For example, an animal study by Fitzgerald et al. with 160 mice showed that low doses of donepezil (0.02 to 0.2 mg/kg) had antidepressant properties (approximately equivalent to the usual dose of 5 - 10 mg/day for humans) and higher doses (2 mg/kg) had depression-like effects (Table 1) (39, 80).

The action mechanism of AChEIs, especially donepezil, in mood disorders and depression is unclear and seems complicated. However, according to studies, various mechanisms, such as the antidepressant effect of donepezil via the sigma-1 receptor, the anxiolytic, anhedonic, and antidepressant effect of this drug through nicotinic acetylcholine receptors, and regulation and interaction with other neurotransmitters like dopamine and serotonin have been suggested as possible mechanisms (Figure 2) (13, 81, 84).

Another application of donepezil in mood disorders includes improving cognitive impairment caused by selective serotonin reuptake inhibitors (SSRIs). A clinical trial study by Hosseini et al. examining the efficacy of donepezil in improving cognitive impairment induced by citalopram, sertraline, and fluoxetine in depressed patients aged 20 to 50 years confirms this effect (Table 1) (40). Altogether, it seems that donepezil can affect mood disorders differently, but more studies are needed for more accurate and comprehensive conclusions.

2.2.4. Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disease that has various degrees characterized by symptoms such as poor communication and social interaction, limited and repetitive interests and behaviors, language skill problems, and cognitive impairments (42, 85, 86). Even though medications like risperidone, atomoxetine, aripiprazole, and SSRIs have been approved and are already in use, they are not considered successful in alleviating the core symptoms of the disease. On the other hand, this disease's risk factors and pathophysiology are not known precisely, but it seems that various genetic and environmental factors are influential (42, 85, 87). Therefore, studies on the pathophysiology and drugs affecting this disease are still ongoing. Hence, donepezil is one of the candidate drugs that can be effective in improving the

symptoms of this disease by some mechanisms (41, 42, 75).

A study by Karvat and Kimchi examined the effect of donepezil systematically (intraperitoneally) and directly injected into the dorsomedial striatum (DMS) (which is equivalent to the caudate nucleus in humans) on autism-related behaviors in BTBR T + tf/J mice (whose symptoms were very similar to autistic patients). They found that systemic administration of donepezil could improve performance, social interaction, and cognitive flexibility dose-dependently. It was also found that direct administration of DMS improved cognitive flexibility and social factors in autistic mice (85). In another animal study by Kim et al., which examined the effect of subchronic use of donepezil on behaviors and symptoms of valproic acid-induced autistic mice, donepezil could significantly improve the symptoms and behaviors of autistic mice, such as abnormal social behaviors and repetitive behaviors, hyperactivity, and cognitive inflexibility (87). A clinical trial study by Gabis et al., which examined the effect of a combination of donepezil and choline for 12 weeks compared with a placebo on language skills improvement among 60 people with autism aged 5 to 16 years, found that the combination has a significant effect on autistic children under 10 years old compared to the placebo. While the drug was safe regarding side effects, it significantly improved language skills (41). A systematic review by Rossignol and Frye which analyzed the effect of anti-Alzheimer's drugs on the treatment of autism core symptoms, showed that donepezil had an improvement role in some studies (five out of seven studies). Nevertheless, due to contradictory results and differences in the evidence level of studies, no definite conclusion was reached (Table 1) (42).

Defects in the cholinergic system play a fundamental role in the pathophysiology of autism. Histological studies of dead autistic people, for example, have shown a reduction in nicotinic and muscarinic receptors in the parietal, frontal, and temporal cortices, thalamus, and hippocampus. Radiological studies have shown similar results. Therefore, it seems that donepezil can improve the symptoms of autism by regulating acetylcholinesterase and affecting acetylcholine and cholinergic receptors (41, 42, 85, 87).

According to studies, another proposed treatment for ASD is a change in the state of the brain to hypomania because the pathophysiology and symptoms of the two diseases are opposite in many aspects. For example, ASD has low social engagement, low cerebral vasopressin, high cortisol, and low mirror neuron activity, but mania, particularly hypomania, has the reverse characteristic (88). On the other hand, donepezil has been shown in certain studies to produce hypomania by altering the ratio of acetylcholine to dopamine and binding to nicotinic receptors. There-

fore, it seems that this effect as one of the possible mechanisms of donepezil for improving ASD needs further investigation (88-91).

2.2.5. Immune System and Infectious Disease

According to studies, in addition to therapeutic applications in neurological and psychiatric diseases, donepezil can have different effects on the immune system through different mechanisms. Donepezil can affect innate and acquired immune systems through different pathways (14, 92, 93).

Studies show that the cholinergic system plays a role in regulating the immune system and the inflammatory processes. For example, the cholinergic anti-inflammatory pathway (CAP), the efferent branch of the brain-immune loop, initiates anti-inflammatory responses and modulates inflammation from various pathways by secreting acetylcholine. Acetylcholine reduces the production of inflammatory cytokines via modulating nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) gene expression in macrophage cells, which play a fundamental role in the immune system's response to pathogens and inflammatory processes by binding to the alpha-7 nicotinic receptors on these cells. Acetylcholine also modulates the immune system and reduces neutrophil leakage by binding to muscarinic receptors in many cell populations (Figure 1) (14, 92, 94-96).

Besides, studies indicated the anti-inflammatory and neuroprotective effects of donepezil. Evidence shows that 5 - 20 μ M donepezil influences microglial cells and suppresses their inflammatory activation. In addition, the CAP has a major role in these effects. Furthermore, the decline of the microglial production of NO and TNF- α and suppression of iNOS, IL-1 β , and TNF- α gene expression by donepezil were reported. It seems that suppression of microglial activation by donepezil is independent of acetylcholine and its receptor (Figure 1) (97).

On the other hand, in many neurodegenerative, autoimmune, and inflammatory diseases, the balance of the innate immune system and its components, such as cytokines, is disturbed. Sochocka et al., in an in vitro study, investigated the effect of different doses of donepezil on different innate immune mechanisms, such as resistance of peripheral blood leukocytes (PBLs) to viruses (by examining the replication of vesicular stomatitis virus (VSV) and herpesvirus type 1 (HSV-1) in cell lines taken from healthy and AD patients at different ages) and the production of cytokines (by direct measurement of cytokines such as IFNs and TNF- α , as well as the activation of NF- κ B signaling, which regulates cytokine secretion, by immunocytochemical staining). They found that donepezil had a regulatory role in the innate immune system and could affect the an-

tiviral resistance of PBLs, especially in the leukocytes of healthy individuals, and the production and secretion of cytokines in the leukocytes of both healthy individuals and Alzheimer's patients (98, 99). In addition, a similar study studied the effect of two drugs, Ginkgo biloba special extract (EGb 761) and donepezil, both used for AD treatment, on innate immunity mechanisms, including natural antiviral resistance of human leukocytes in vitro and NF- κ B activation. Thirty healthy blood samples were collected from 15 individuals with resistant leukocytes to VSV and 15 individuals with sensitive leukocytes. It was found that 10 - 50 μ g/mL donepezil and 25 - 100 μ g/mL EGb761 increased the resistance of human leukocytes and reduced the activation of transcriptional factor NF- κ B. Furthermore, a relationship was seen between NF- κ B activation and the level of leukocyte resistance (Table 1) (Figure 1) (44).

According to studies, the cholinergic system seems to play an influential role in modulating lung inflammation, especially in infections, and maintaining normal lung function. Increased secretion of acetylcholine following lung inflammation can help modulate inflammation and repair damaged lung tissue by various pathways, such as shifting the macrophages population to M2 macrophages, which secrete anti-inflammatory cytokines and play an anti-inflammatory role in inflammatory processes, regulating the differentiation and growth of airway cells to improve the function of the epithelium of these ducts, which are altered by inflammatory cytokines, reducing neutrophil leakage from these ducts, and increasing cholinergic lymphocytes in the lungs, which play an influential role in regulating inflammatory processes (Figure 1) (14). A retrospective study by Abe et al. also showed this effect. This research, which analyzed the data from 25,602 elderly hospitalized in Japan for almost two years with a diagnosis of pneumonia, revealed that donepezil decreased death by 64%. People receiving donepezil for dementia (about 578 individuals) showed considerably lower death rates than those with dementia who did not take donepezil and those without dementia. Therefore, this drug, which increases acetylcholine levels, was considered an independent factor in reducing pneumonia mortality among the elderly in this study, consistent with previous studies (Table 1) (43).

Moreover, patients treated with donepezil showed declined death risk from pneumonia and myocardial infarct, increased vascular function, and suppressed stroke risk. The studies showed that fatal acute respiratory distress syndrome (ARDS), sepsis, cytokine storm, cardiovascular damage, disseminated intravascular coagulation (DIC), and acute kidney damage could be inhibited via this drug. These effects seem to be due to the immunomodulatory effects of donepezil on innate and acquired immune systems

(14).

Similarly, a decline in the risk of death was reported in patients treated with donepezil after COVID-19 infection. In addition to the mechanisms mentioned above, this effect appears to be due to the effects of donepezil on the sigma-1 receptor (14). Coronaviruses replicate in an altered membrane portion of the endoplasmic reticulum (ER), contribute to ER stress in the host cell, and activate pathways to accommodate the host cells for viral demands. The regulation of ER remodeling and ER stress response may play a significant role in virus-host interaction and infection treatment. Consequently, the sigma-1 receptor (Sig-1R), a membrane chaperon with an upstream modulatory function in ER stress, has been studied as a potential treatment for COVID-19 patients. Sig-1R modulates vital mechanisms of the adaptive host cell stress response and is involved in the early steps of viral replication. Using Sig-1R as a target in therapeutic approaches seems not to decrease viral replication. However, it might be a cross-reaction with early steps of virus-induced host cell reprogramming, helping decline the course of infection, inhibiting the severity of the disease, or even making a chance to develop a preventive immune response. Therefore, it seems that drugs, such as fluvoxamine, donepezil, and hydroxychloroquine, which have relatively good binding to this receptor, can be effective in modulating and treating the disease through mechanisms such as inhibiting the interaction of virus proteins with this receptor and subsequently inhibiting intracellular signaling (Figure 1) (100, 101).

There are also similarities between the pathophysiology of AD and COVID-19. In both diseases, inflammatory processes, such as increased proinflammatory cytokines like IL-1 and IL-6 and increased cytoskeleton-associated protein 4 (CKAP4) and galectin-9 (GAL-9), are seen (102). Therefore, it seems that donepezil, due to its immunomodulatory effects on the pathophysiology of AD, as described in detail in the section "AD and donepezil," can be effective in treating COVID-19. However, more preclinical and clinical studies are needed (102).

2.3. Current Challenges and Future Prospects of Donepezil

Donepezil is an important cholinesterase inhibitor for treating AD, but its therapeutic efficacy varies from 20 - 60%, and patients with AD respond differently to it. Various studies showed that genetic factors affect pharmacokinetics and pharmacodynamics differently, leading to different clinical efficacies. Several studies indicated the association between the therapeutic efficacy of donepezil and hepatic enzymes gene polymorphisms like CYP2D6 and CYP3A4 (7). Apolipoprotein E (APOE) alleles like APOE E3 also affect the efficacy of donepezil. Therefore, these personal differences

must be considered for achieving better clinical outcomes (7).

Another challenge in treating diseases like AD is their different symptoms and pathways. Therefore, it is necessary to use diverse drug combinations to control the disease, which could reduce the capacity of patients and increase side effects and drug interactions. Various studies have been conducted to design new derivatives of donepezil to affect different receptors and pathways. The benzylpiperidine and dimethoxy indanone are components of the donepezil structure that could bind to or replace with compounds such as pyridyl methyl piperidine, benzylpiperazine, pyrimidyl piperazine, heterocyclic rings, ferulic acid, flavonoids, and curcumin, making derivatives with new properties such as anti-oxidative, anti-dementia, and monoamine oxidase inhibition-like effects (4). Therefore, more studies are needed to obtain better therapeutic responses and fewer side effects in the future.

3. Conclusions

Although many studies have emphasized the efficacy of donepezil in treating AD, various clinical and preclinical studies showed that it could positively affect other dementias, such as Parkinson's disease, vascular dementia, and other neurological, psychiatric, and even infectious diseases. These effects of donepezil seem to be exerted through other mechanisms like sigma-1 receptor and cholinergic receptors signaling activation and inflammation processes modulation, in addition to inhibiting AChE and increasing acetylcholine.

In general, more comprehensive and accurate studies are needed to make better decisions about the efficacy of this drug in other diseases. It is also recommended to consider personal differences in clinical responses and apply new derivations with multi-efficacy in further studies.

Footnotes

Authors' Contribution: Study concept and design: P. P., and M. S. Analysis and interpretation of data: P. P., and M. S. Drafting of the manuscript: P. P., M. S., S. SM., and A. T. Critical revision of the manuscript for important intellectual content: M. S., S. SM., and A. T.

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References

- Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev.* 2018;(6). CD001190. doi: [10.1002/14651858.CD001190.pub3](https://doi.org/10.1002/14651858.CD001190.pub3). [PubMed: [29923184](https://pubmed.ncbi.nlm.nih.gov/29923184/)]. [PubMed Central: [PMC6513124](https://pubmed.ncbi.nlm.nih.gov/PMC6513124/)].
- Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. *Curr Neuropharmacol.* 2013;**11**(3):315–35. doi: [10.2174/1570159X110300006](https://doi.org/10.2174/1570159X110300006). [PubMed: [24179466](https://pubmed.ncbi.nlm.nih.gov/24179466/)]. [PubMed Central: [PMC3648782](https://pubmed.ncbi.nlm.nih.gov/PMC3648782/)].
- National Center for Biotechnology Information. *PubChem Compound Summary for CID 5741, Donepezil hydrochloride*. National Center for Biotechnology Information; 2022, [cited June 30, 2022]. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Donepezil-hydrochloride>.
- Mohsin NUA, Ahmad M. Donepezil: A review of the recent structural modifications and their impact on anti-Alzheimer activity. *Braz J Pharm Sci.* 2020;**56**. e18325. doi: [10.1590/s2175-97902019000418325](https://doi.org/10.1590/s2175-97902019000418325).
- Jelic V, Darreh-Shori T. Donepezil: A Review of Pharmacological Characteristics and Role in the Management of Alzheimer Disease. *Clin Med Insights Ther.* 2010;**2**:CMT.S5410. doi: [10.4137/cmt.s5410](https://doi.org/10.4137/cmt.s5410).
- Sharma K. Cholinesterase inhibitors as Alzheimer's therapeutics (Review). *Mol Med Rep.* 2019;**20**(2):1479–87. doi: [10.3892/mmr.2019.10374](https://doi.org/10.3892/mmr.2019.10374). [PubMed: [31257471](https://pubmed.ncbi.nlm.nih.gov/31257471/)]. [PubMed Central: [PMC6625431](https://pubmed.ncbi.nlm.nih.gov/PMC6625431/)].
- Lu J, Wang X, Wan L, Fu J, Huo Y, Zhao Y, et al. Gene Polymorphisms Affecting the Pharmacokinetics and Pharmacodynamics of Donepezil Efficacy. *Front Pharmacol.* 2020;**11**:934. doi: [10.3389/fphar.2020.00934](https://doi.org/10.3389/fphar.2020.00934). [PubMed: [32636753](https://pubmed.ncbi.nlm.nih.gov/32636753/)]. [PubMed Central: [PMC7317019](https://pubmed.ncbi.nlm.nih.gov/PMC7317019/)].
- Seltzer B. Donepezil: an update. *Expert Opin Pharmacother.* 2007;**8**(7):1011–23. doi: [10.1517/14656566.8.7.1011](https://doi.org/10.1517/14656566.8.7.1011). [PubMed: [17472546](https://pubmed.ncbi.nlm.nih.gov/17472546/)].
- Sutthapitaksakul L, Dass CR, Sriamornsak P. Donepezil—an updated review of challenges in dosage form design. *J Drug Deliv Sci Technol.* 2021;**63**:102549. doi: [10.1016/j.jddst.2021.102549](https://doi.org/10.1016/j.jddst.2021.102549).
- Adlimgoddam A, Neuendorff M, Roy B, Albensi BC. A review of clinical treatment considerations of donepezil in severe Alzheimer's disease. *CNS Neurosci Ther.* 2018;**24**(10):876–88. doi: [10.1111/cns.13035](https://doi.org/10.1111/cns.13035). [PubMed: [30058285](https://pubmed.ncbi.nlm.nih.gov/30058285/)]. [PubMed Central: [PMC6489741](https://pubmed.ncbi.nlm.nih.gov/PMC6489741/)].
- Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K, et al. Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primers.* 2021;**7**(1):47. doi: [10.1038/s41572-021-00280-3](https://doi.org/10.1038/s41572-021-00280-3). [PubMed: [34210995](https://pubmed.ncbi.nlm.nih.gov/34210995/)].
- Chen JH, Huang TW, Hong CT. Cholinesterase inhibitors for gait, balance, and fall in Parkinson disease: a meta-analysis. *NPJ Parkinsons Dis.* 2021;**7**(1):103. doi: [10.1038/s41531-021-00251-1](https://doi.org/10.1038/s41531-021-00251-1). [PubMed: [34824258](https://pubmed.ncbi.nlm.nih.gov/34824258/)]. [PubMed Central: [PMC8617004](https://pubmed.ncbi.nlm.nih.gov/PMC8617004/)].
- Walczak-Nowicka LJ, Herbet M. Acetylcholinesterase Inhibitors in the Treatment of Neurodegenerative Diseases and the Role of Acetylcholinesterase in their Pathogenesis. *Int J Mol Sci.* 2021;**22**(17):9290. doi: [10.3390/ijms22179290](https://doi.org/10.3390/ijms22179290). [PubMed: [34502198](https://pubmed.ncbi.nlm.nih.gov/34502198/)]. [PubMed Central: [PMC8430571](https://pubmed.ncbi.nlm.nih.gov/PMC8430571/)].
- Murali MM, Phillips JA. Repurposing Donepezil to Treat COVID-19: A Call for Retrospective Analysis of Existing Patient Datasets. *J Clin Immunol Microbiol.* 2021;**2**(3):1–12. doi: [10.46889/jcim.2021.2305](https://doi.org/10.46889/jcim.2021.2305).
- Jacobson SA, Sabbagh MN. Donepezil: potential neuroprotective and disease-modifying effects. *Expert Opin Drug Metab Toxicol.* 2008;**4**(10):1363–9. doi: [10.1517/17425255.4.10.1363](https://doi.org/10.1517/17425255.4.10.1363). [PubMed: [18798705](https://pubmed.ncbi.nlm.nih.gov/18798705/)].

16. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7(2):e105–25. doi: [10.1016/S2468-2667\(21\)00249-8](https://doi.org/10.1016/S2468-2667(21)00249-8). [PubMed: [34998485](https://pubmed.ncbi.nlm.nih.gov/34998485/)]. [PubMed Central: [PMC8810394](https://pubmed.ncbi.nlm.nih.gov/PMC8810394/)].
17. Dong H, Yuede CM, Coughlan CA, Murphy KM, Csernansky JG. Effects of donepezil on amyloid-beta and synapse density in the Tg2576 mouse model of Alzheimer's disease. *Brain Res*. 2009;1303:169–78. doi: [10.1016/j.brainres.2009.09.097](https://doi.org/10.1016/j.brainres.2009.09.097). [PubMed: [19799879](https://pubmed.ncbi.nlm.nih.gov/19799879/)]. [PubMed Central: [PMC2789417](https://pubmed.ncbi.nlm.nih.gov/PMC2789417/)].
18. Kim SH, Kandiah N, Hsu JL, Suthisisang C, Udommongkol C, Dash A. Beyond symptomatic effects: potential of donepezil as a neuroprotective agent and disease modifier in Alzheimer's disease. *Br J Pharmacol*. 2017;174(23):4224–32. doi: [10.1111/bph.14030](https://doi.org/10.1111/bph.14030). [PubMed: [28901528](https://pubmed.ncbi.nlm.nih.gov/28901528/)]. [PubMed Central: [PMC5715569](https://pubmed.ncbi.nlm.nih.gov/PMC5715569/)].
19. Kim HG, Moon M, Choi JG, Park G, Kim AJ, Hur J, et al. Donepezil inhibits the amyloid-beta oligomer-induced microglial activation in vitro and in vivo. *Neurotoxicology*. 2014;40:23–32. doi: [10.1016/j.neuro.2013.10.004](https://doi.org/10.1016/j.neuro.2013.10.004). [PubMed: [24189446](https://pubmed.ncbi.nlm.nih.gov/24189446/)].
20. Yoshiyama Y, Kojima A, Ishikawa C, Arai K. Anti-inflammatory action of donepezil ameliorates tau pathology, synaptic loss, and neurodegeneration in a tauopathy mouse model. *J Alzheimers Dis*. 2010;22(1):295–306. doi: [10.3233/JAD-2010-100681](https://doi.org/10.3233/JAD-2010-100681). [PubMed: [20847440](https://pubmed.ncbi.nlm.nih.gov/20847440/)].
21. Shen H, Kihara T, Hongo H, Wu X, Kem WR, Shimohama S, et al. Neuroprotection by donepezil against glutamate excitotoxicity involves stimulation of alpha7 nicotinic receptors and internalization of NMDA receptors. *Br J Pharmacol*. 2010;161(1):127–39. doi: [10.1111/j.1476-5381.2010.00894.x](https://doi.org/10.1111/j.1476-5381.2010.00894.x). [PubMed: [20718745](https://pubmed.ncbi.nlm.nih.gov/20718745/)]. [PubMed Central: [PMC2962822](https://pubmed.ncbi.nlm.nih.gov/PMC2962822/)].
22. Sharma K, Pradhan S, Duffy LK, Yeasmin S, Bhattarai N, Schulte MK. Role of Receptors in Relation to Plaques and Tangles in Alzheimer's Disease Pathology. *Int J Mol Sci*. 2021;22(23):12987. doi: [10.3390/ijms222312987](https://doi.org/10.3390/ijms222312987). [PubMed: [34884789](https://pubmed.ncbi.nlm.nih.gov/34884789/)]. [PubMed Central: [PMC8657621](https://pubmed.ncbi.nlm.nih.gov/PMC8657621/)].
23. Jiang L, Wang Y, Su L, Ren H, Wang C, Chen J, et al. Donepezil Attenuates Obesity-Associated Oxidative Stress and Central Inflammation and Improves Memory Deficit in Mice Fed a High-Fat Diet. *Dement Geriatr Cogn Disord*. 2019;48(3-4):154–63. doi: [10.1159/000504800](https://doi.org/10.1159/000504800). [PubMed: [31940604](https://pubmed.ncbi.nlm.nih.gov/31940604/)].
24. Umukoro S, Adewole FA, Eduviere AT, Aderibigbe AO, Onwuchekwa C. Free radical scavenging effect of donepezil as the possible contribution to its memory enhancing activity in mice. *Drug Res (Stuttg)*. 2014;64(5):236–9. doi: [10.1055/s-0033-1357126](https://doi.org/10.1055/s-0033-1357126). [PubMed: [24203083](https://pubmed.ncbi.nlm.nih.gov/24203083/)].
25. Jin JL, Fang M, Zhao YX, Liu XY. Roles of sigma-1 receptors in Alzheimer's disease. *Int J Clin Exp Med*. 2015;8(4):4808–20. [PubMed: [26131055](https://pubmed.ncbi.nlm.nih.gov/26131055/)]. [PubMed Central: [PMC4484039](https://pubmed.ncbi.nlm.nih.gov/PMC4484039/)].
26. Ryskamp DA, Korban S, Zhemkov V, Kraskovskaya N, Bezprozvanny I. Neuronal Sigma-1 Receptors: Signaling Functions and Protective Roles in Neurodegenerative Diseases. *Front Neurosci*. 2019;13:862. doi: [10.3389/fnins.2019.00862](https://doi.org/10.3389/fnins.2019.00862). [PubMed: [31551669](https://pubmed.ncbi.nlm.nih.gov/31551669/)]. [PubMed Central: [PMC6736580](https://pubmed.ncbi.nlm.nih.gov/PMC6736580/)].
27. Bond M, Rogers G, Peters J, Anderson R, Hoyle M, Miners A, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. *Health Technol Assess*. 2012;16(21):1–470. doi: [10.3310/hta16210](https://doi.org/10.3310/hta16210). [PubMed: [22541366](https://pubmed.ncbi.nlm.nih.gov/22541366/)]. [PubMed Central: [PMC4780923](https://pubmed.ncbi.nlm.nih.gov/PMC4780923/)].
28. Li DD, Zhang YH, Zhang W, Zhao P. Meta-Analysis of Randomized Controlled Trials on the Efficacy and Safety of Donepezil, Galantamine, Rivastigmine, and Memantine for the Treatment of Alzheimer's Disease. *Front Neurosci*. 2019;13:472. doi: [10.3389/fnins.2019.00472](https://doi.org/10.3389/fnins.2019.00472). [PubMed: [31156366](https://pubmed.ncbi.nlm.nih.gov/31156366/)]. [PubMed Central: [PMC6529534](https://pubmed.ncbi.nlm.nih.gov/PMC6529534/)].
29. Zhang N, Gordon ML. Clinical efficacy and safety of donepezil in the treatment of Alzheimer's disease in Chinese patients. *Clin Interv Aging*. 2018;13:1963–70. doi: [10.2147/CIA.S159920](https://doi.org/10.2147/CIA.S159920). [PubMed: [30349215](https://pubmed.ncbi.nlm.nih.gov/30349215/)]. [PubMed Central: [PMC6187917](https://pubmed.ncbi.nlm.nih.gov/PMC6187917/)].
30. Doody RS, Cummings JL, Farlow MR. Reviewing the role of donepezil in the treatment of Alzheimer's disease. *Curr Alzheimer Res*. 2012;9(7):773–81. doi: [10.2174/156720512802455412](https://doi.org/10.2174/156720512802455412). [PubMed: [22175653](https://pubmed.ncbi.nlm.nih.gov/22175653/)].
31. Prvulovic D, Schneider B. Pharmacokinetic and pharmacodynamic evaluation of donepezil for the treatment of Alzheimer's disease. *Expert Opin Drug Metab Toxicol*. 2014;10(7):1039–50. doi: [10.1517/17425255.2014.915028](https://doi.org/10.1517/17425255.2014.915028). [PubMed: [24785550](https://pubmed.ncbi.nlm.nih.gov/24785550/)].
32. Wang HF, Yu JT, Tang SW, Jiang T, Tan CC, Meng XF, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. *J Neurol Neurosurg Psychiatry*. 2015;86(2):135–43. doi: [10.1136/jnnp-2014-307659](https://doi.org/10.1136/jnnp-2014-307659). [PubMed: [24828899](https://pubmed.ncbi.nlm.nih.gov/24828899/)].
33. Kim JO, Lee SJ, Pyo JS. Effect of acetylcholinesterase inhibitors on post-stroke cognitive impairment and vascular dementia: A meta-analysis. *PLoS One*. 2020;15(2). e0227820. doi: [10.1371/journal.pone.0227820](https://doi.org/10.1371/journal.pone.0227820). [PubMed: [32032361](https://pubmed.ncbi.nlm.nih.gov/32032361/)]. [PubMed Central: [PMC7006920](https://pubmed.ncbi.nlm.nih.gov/PMC7006920/)].
34. Battle CE, Abdul-Rahim AH, Shenkin SD, Hewitt J, Quinn TJ. Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;(2). CD013306. doi: [10.1002/14651858.CD013306.pub2](https://doi.org/10.1002/14651858.CD013306.pub2). [PubMed: [33704781](https://pubmed.ncbi.nlm.nih.gov/33704781/)]. [PubMed Central: [PMC8407366](https://pubmed.ncbi.nlm.nih.gov/PMC8407366/)].
35. Wheaton P, Mathias JL, Vink R. Impact of pharmacological treatments on cognitive and behavioral outcome in the postacute stages of adult traumatic brain injury: a meta-analysis. *J Clin Psychopharmacol*. 2011;31(6):745–57. doi: [10.1097/JCP.0b013e318235f4ac](https://doi.org/10.1097/JCP.0b013e318235f4ac). [PubMed: [22020351](https://pubmed.ncbi.nlm.nih.gov/22020351/)].
36. Campbell KA, Kennedy RE, Brunner RC, Hollis SD, Lumsden RA, Novack TA. The effect of donepezil on the cognitive ability early in the course of recovery from traumatic brain injury. *Brain Inj*. 2018;32(8):972–9. doi: [10.1080/02699052.2018.1468574](https://doi.org/10.1080/02699052.2018.1468574). [PubMed: [29737870](https://pubmed.ncbi.nlm.nih.gov/29737870/)].
37. Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. *Neurology*. 2010;75(14):1263–9. doi: [10.1212/WNL.0b013e318f16128c](https://doi.org/10.1212/WNL.0b013e318f16128c). [PubMed: [20810998](https://pubmed.ncbi.nlm.nih.gov/20810998/)]. [PubMed Central: [PMC3013493](https://pubmed.ncbi.nlm.nih.gov/PMC3013493/)].
38. Reynolds CR, Butters MA, Lopez O, Pollock BG, Dew MA, Mulsant BH, et al. Maintenance treatment of depression in old age: a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. *Arch Gen Psychiatry*. 2011;68(1):51–60. doi: [10.1001/archgenpsychiatry.2010.184](https://doi.org/10.1001/archgenpsychiatry.2010.184). [PubMed: [21199965](https://pubmed.ncbi.nlm.nih.gov/21199965/)]. [PubMed Central: [PMC3076045](https://pubmed.ncbi.nlm.nih.gov/PMC3076045/)].
39. Fitzgerald PJ, Hale PJ, Ghimire A, Watson BO. The cholinesterase inhibitor donepezil has antidepressant-like properties in the mouse forced swim test. *Transl Psychiatry*. 2020;10(1):255. doi: [10.1038/s41398-020-00928-w](https://doi.org/10.1038/s41398-020-00928-w). [PubMed: [32712627](https://pubmed.ncbi.nlm.nih.gov/32712627/)]. [PubMed Central: [PMC7382650](https://pubmed.ncbi.nlm.nih.gov/PMC7382650/)].
40. Hosseini F, Nadi M, Kiani M, Shahzedei S. [Effect of Donepezil on Cognitive Disorders Due to the Selective Serotonin Reuptake Inhibitors in the Patients with Major Depressive Disorder]. *J Shahid Sadoughi Univ Med Sci*. 2020;27(10):2017–26. Persian. doi: [10.18502/ssu.v27i10.2407](https://doi.org/10.18502/ssu.v27i10.2407).
41. Gabis LV, Ben-Hur R, Shefer S, Jokel A, Shalom DB. Improvement of Language in Children with Autism with Combined Donepezil and Choline Treatment. *J Mol Neurosci*. 2019;69(2):224–34. doi: [10.1007/s12031-019-01351-7](https://doi.org/10.1007/s12031-019-01351-7). [PubMed: [31230222](https://pubmed.ncbi.nlm.nih.gov/31230222/)].
42. Rossignol DA, Frye RE. The Use of Medications Approved for Alzheimer's Disease in Autism Spectrum Disorder: A Systematic Review. *Front Pediatr*. 2014;2:87. doi: [10.3389/fped.2014.00087](https://doi.org/10.3389/fped.2014.00087).
43. Abe Y, Shimokado K, Fushimi K. Donepezil is associated with decreased in-hospital mortality as a result of pneumonia among older patients with dementia: A retrospective cohort study. *Geriatr Gerontol Int*. 2018;18(2):269–75. doi: [10.1111/ggi.13177](https://doi.org/10.1111/ggi.13177). [PubMed: [29139192](https://pubmed.ncbi.nlm.nih.gov/29139192/)].
44. Sochocka M, Zaczynska E, Tabol A, Czarny A, Leszek J, Sobczynski M.

- The influence of donepezil and EGb 761 on the innate immunity of human leukocytes: effect on the NF-kappaB system. *Int Immunopharmacol*. 2010;**10**(12):1505-13. doi: [10.1016/j.intimp.2010.08.024](https://doi.org/10.1016/j.intimp.2010.08.024). [PubMed: [20837172](https://pubmed.ncbi.nlm.nih.gov/20837172/)].
45. Fang C, Lv L, Mao S, Dong H, Liu B. Cognition Deficits in Parkinson's Disease: Mechanisms and Treatment. *Parkinsons Dis*. 2020;**2020**:2076942. doi: [10.1155/2020/2076942](https://doi.org/10.1155/2020/2076942). [PubMed: [32269747](https://pubmed.ncbi.nlm.nih.gov/32269747/)]. [PubMed Central: [PMC7128056](https://pubmed.ncbi.nlm.nih.gov/PMC7128056/)].
 46. Dalrymple-Alford JC, Livingston L, MacAskill MR, Graham C, Melzer TR, Porter RJ, et al. Characterizing mild cognitive impairment in Parkinson's disease. *Mov Disord*. 2011;**26**(4):629-36. doi: [10.1002/mds.23592](https://doi.org/10.1002/mds.23592). [PubMed: [21287603](https://pubmed.ncbi.nlm.nih.gov/21287603/)].
 47. Yarnall AJ, Breen DP, Duncan GW, Khoo TK, Coleman SY, Firbank MJ, et al. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. *Neurology*. 2014;**82**(4):308-16. doi: [10.1212/WNL.000000000000066](https://doi.org/10.1212/WNL.000000000000066). [PubMed: [24363137](https://pubmed.ncbi.nlm.nih.gov/24363137/)]. [PubMed Central: [PMC3929202](https://pubmed.ncbi.nlm.nih.gov/PMC3929202/)].
 48. Gratwicke J, Jahanshahi M, Foltyniec T. Parkinson's disease dementia: a neural networks perspective. *Brain*. 2015;**138**(Pt 6):1454-76. doi: [10.1093/brain/awv104](https://doi.org/10.1093/brain/awv104). [PubMed: [25888551](https://pubmed.ncbi.nlm.nih.gov/25888551/)]. [PubMed Central: [PMC4614131](https://pubmed.ncbi.nlm.nih.gov/PMC4614131/)].
 49. Dubois B, Tolosa E, Katzschlager R, Emre M, Lees AJ, Schumann G, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. *Mov Disord*. 2012;**27**(10):1230-8. doi: [10.1002/mds.25098](https://doi.org/10.1002/mds.25098). [PubMed: [22915447](https://pubmed.ncbi.nlm.nih.gov/22915447/)].
 50. Skrobot OA, O'Brien J, Black S, Chen C, DeCarli C, Erkinjuntti T, et al. The Vascular Impairment of Cognition Classification Consensus Study. *Alzheimers Dement*. 2017;**13**(6):624-33. doi: [10.1016/j.jalz.2016.10.007](https://doi.org/10.1016/j.jalz.2016.10.007). [PubMed: [27960092](https://pubmed.ncbi.nlm.nih.gov/27960092/)].
 51. Sharma B, Singh N. Experimental hypertension induced vascular dementia: pharmacological, biochemical and behavioral recuperation by angiotensin receptor blocker and acetylcholinesterase inhibitor. *Pharmacol Biochem Behav*. 2012;**102**(1):101-8. doi: [10.1016/j.pbb.2012.03.029](https://doi.org/10.1016/j.pbb.2012.03.029). [PubMed: [22507914](https://pubmed.ncbi.nlm.nih.gov/22507914/)].
 52. Jian WX, Zhang Z, Zhan JH, Chu SF, Peng Y, Zhao M, et al. Donepezil attenuates vascular dementia in rats through increasing BDNF induced by reducing HDAC6 nuclear translocation. *Acta Pharmacol Sin*. 2020;**41**(5):588-98. doi: [10.1038/s41401-019-0334-5](https://doi.org/10.1038/s41401-019-0334-5). [PubMed: [31913348](https://pubmed.ncbi.nlm.nih.gov/31913348/)]. [PubMed Central: [PMC7470853](https://pubmed.ncbi.nlm.nih.gov/PMC7470853/)].
 53. Knight R, Khondoker M, Magill N, Stewart R, Landau S. A Systematic Review and Meta-Analysis of the Effectiveness of Acetylcholinesterase Inhibitors and Memantine in Treating the Cognitive Symptoms of Dementia. *Dement Geriatr Cogn Disord*. 2018;**45**(3-4):131-51. doi: [10.1159/000486546](https://doi.org/10.1159/000486546). [PubMed: [29734182](https://pubmed.ncbi.nlm.nih.gov/29734182/)].
 54. Wu PH, Lin YT, Hsu PC, Yang YH, Lin TH, Huang CT. Impact of acetylcholinesterase inhibitors on the occurrence of acute coronary syndrome in patients with dementia. *Sci Rep*. 2015;**5**:15451. doi: [10.1038/srep15451](https://doi.org/10.1038/srep15451). [PubMed: [26577589](https://pubmed.ncbi.nlm.nih.gov/26577589/)]. [PubMed Central: [PMC4649673](https://pubmed.ncbi.nlm.nih.gov/PMC4649673/)].
 55. Mufti M, Stabile M, Amico J. What is the efficacy of donepezil in patients with vascular dementia? *Evidence-Based Practice*. 2019;**22**(12):31. doi: [10.1097/ebp.0000000000000449](https://doi.org/10.1097/ebp.0000000000000449).
 56. Bengtsson M, Godbolt AK. Effects of acetylcholinesterase inhibitors on cognitive function in patients with chronic traumatic brain injury: A systematic review. *J Rehabil Med*. 2016;**48**(1):1-5. doi: [10.2340/16501977-2040](https://doi.org/10.2340/16501977-2040). [PubMed: [26660510](https://pubmed.ncbi.nlm.nih.gov/26660510/)].
 57. Shively S, Scher AI, Perl DP, Diaz-Arrastia R. Dementia resulting from traumatic brain injury: what is the pathology? *Arch Neurol*. 2012;**69**(10):1245-51. doi: [10.1001/archneurol.2011.3747](https://doi.org/10.1001/archneurol.2011.3747). [PubMed: [22776913](https://pubmed.ncbi.nlm.nih.gov/22776913/)]. [PubMed Central: [PMC3716376](https://pubmed.ncbi.nlm.nih.gov/PMC3716376/)].
 58. Scher LM, Loomis E, McCarron RM. Traumatic brain injury: Pharmacotherapy options for cognitive deficits. *Curr Psychiatry*. 2011;**10**(2):21-37.
 59. Rabinowitz AR, Watanabe TK. Pharmacotherapy for Treatment of Cognitive and Neuropsychiatric Symptoms After mTBI. *J Head Trauma Rehabil*. 2020;**35**(1):76-83. doi: [10.1097/HTR.0000000000000537](https://doi.org/10.1097/HTR.0000000000000537). [PubMed: [31834058](https://pubmed.ncbi.nlm.nih.gov/31834058/)]. [PubMed Central: [PMC6940511](https://pubmed.ncbi.nlm.nih.gov/PMC6940511/)].
 60. Wortzel HS, Arciniegas DB. Treatment of post-traumatic cognitive impairments. *Curr Treat Options Neurol*. 2012;**14**(5):493-508. doi: [10.1007/s11940-012-0193-6](https://doi.org/10.1007/s11940-012-0193-6). [PubMed: [22865461](https://pubmed.ncbi.nlm.nih.gov/22865461/)]. [PubMed Central: [PMC3437653](https://pubmed.ncbi.nlm.nih.gov/PMC3437653/)].
 61. Yu TS, Kim A, Kernie SG. Donepezil rescues spatial learning and memory deficits following traumatic brain injury independent of its effects on neurogenesis. *PLoS One*. 2015;**10**(2). e0118793. doi: [10.1371/journal.pone.0118793](https://doi.org/10.1371/journal.pone.0118793). [PubMed: [25714524](https://pubmed.ncbi.nlm.nih.gov/25714524/)]. [PubMed Central: [PMC4340948](https://pubmed.ncbi.nlm.nih.gov/PMC4340948/)].
 62. Shahpouri MM, Barekatin M, Tavakoli M, Mirmosayyeb O, Safaei A, Shayannejad V. Comparison of Cognitive Rehabilitation versus Donepezil Therapy on Memory Performance, Attention, Quality of Life, and Depression among Multiple Sclerosis Patients. *Neuro Res Int*. 2020;**2020**:8874424. doi: [10.1155/2020/8874424](https://doi.org/10.1155/2020/8874424). [PubMed: [33299606](https://pubmed.ncbi.nlm.nih.gov/33299606/)]. [PubMed Central: [PMC7704202](https://pubmed.ncbi.nlm.nih.gov/PMC7704202/)].
 63. O'Carroll CB, Woodruff BK, Locke DE, Hoffman-Snyder CR, Wellik KE, Thayer GM, et al. Is donepezil effective for multiple sclerosis-related cognitive dysfunction? A critically appraised topic. *Neurologist*. 2012;**18**(1):51-4. doi: [10.1097/NRL.0b013e31823fa3ba](https://doi.org/10.1097/NRL.0b013e31823fa3ba). [PubMed: [22217618](https://pubmed.ncbi.nlm.nih.gov/22217618/)].
 64. Kooi EJ, Prins M, Bajic N, Belien JA, Gerritsen WH, van Horsen J, et al. Cholinergic imbalance in the multiple sclerosis hippocampus. *Acta Neuropathol*. 2011;**122**(3):313-22. doi: [10.1007/s00401-011-0849-4](https://doi.org/10.1007/s00401-011-0849-4). [PubMed: [21691765](https://pubmed.ncbi.nlm.nih.gov/21691765/)]. [PubMed Central: [PMC3168443](https://pubmed.ncbi.nlm.nih.gov/PMC3168443/)].
 65. Shahpouri MM, Barekatin M, Tavakoli M, Badihian S, Shayannejad V. Effect of Donepezil on Cognitive Impairment, Quality of Life, and Depression in Multiple Sclerosis Patients: A Randomized Clinical Trial. *Int J Prev Med*. 2020;**11**:69. doi: [10.4103/ijpvm.IJPVM_154_19](https://doi.org/10.4103/ijpvm.IJPVM_154_19). [PubMed: [32742613](https://pubmed.ncbi.nlm.nih.gov/32742613/)]. [PubMed Central: [PMC7373083](https://pubmed.ncbi.nlm.nih.gov/PMC7373083/)].
 66. Zhu W, Zhang Z, Qi J, Liu F, Chen J, Zhao J, et al. Adjunctive treatment for cognitive impairment in patients with chronic schizophrenia: a double-blind, placebo-controlled study. *Neuropsychiatr Dis Treat*. 2014;**10**:1317-23. doi: [10.2147/NDT.S64189](https://doi.org/10.2147/NDT.S64189). [PubMed: [25075190](https://pubmed.ncbi.nlm.nih.gov/25075190/)]. [PubMed Central: [PMC4106965](https://pubmed.ncbi.nlm.nih.gov/PMC4106965/)].
 67. Thakurathi N, Vincenzi B, Henderson DC. Assessing the prospect of donepezil in improving cognitive impairment in patients with schizophrenia. *Expert Opin Investig Drugs*. 2013;**22**(2):259-65. doi: [10.1517/13543784.2013.750650](https://doi.org/10.1517/13543784.2013.750650). [PubMed: [23215841](https://pubmed.ncbi.nlm.nih.gov/23215841/)].
 68. Keefe RS, Malhotra AK, Meltzer HY, Kane JM, Buchanan RW, Murthy A, et al. Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: significant placebo/practice effects in a 12-week, randomized, double-blind, placebo-controlled trial. *Neuropsychopharmacology*. 2008;**33**(6):1217-28. doi: [10.1038/sj.npp.1301499](https://doi.org/10.1038/sj.npp.1301499). [PubMed: [17625502](https://pubmed.ncbi.nlm.nih.gov/17625502/)].
 69. Hsu WY, Lane HY, Lin CH. Medications Used for Cognitive Enhancement in Patients With Schizophrenia, Bipolar Disorder, Alzheimer's Disease, and Parkinson's Disease. *Front Psychiatry*. 2018;**9**:91. doi: [10.3389/fpsy.2018.00091](https://doi.org/10.3389/fpsy.2018.00091). [PubMed: [29670547](https://pubmed.ncbi.nlm.nih.gov/29670547/)]. [PubMed Central: [PMC5893641](https://pubmed.ncbi.nlm.nih.gov/PMC5893641/)].
 70. Stuart S, Morris R, Giritharan A, Quinn J, Nutt JG, Mancini M. Prefrontal Cortex Activity and Gait in Parkinson's Disease With Cholinergic and Dopaminergic Therapy. *Mov Disord*. 2020;**35**(11):2019-27. doi: [10.1002/mds.28214](https://doi.org/10.1002/mds.28214). [PubMed: [32830901](https://pubmed.ncbi.nlm.nih.gov/32830901/)].
 71. Mancini M, Fling BW, Gendreau A, Lapidus J, Horak FB, Chung K, et al. Effect of augmenting cholinergic function on gait and balance. *BMC Neurol*. 2015;**15**:264. doi: [10.1186/s12883-015-0523-x](https://doi.org/10.1186/s12883-015-0523-x). [PubMed: [26697847](https://pubmed.ncbi.nlm.nih.gov/26697847/)]. [PubMed Central: [PMC4690312](https://pubmed.ncbi.nlm.nih.gov/PMC4690312/)].
 72. Ahlsgog JE. Think before you leap: donepezil reduces falls? *Neurology*. 2010;**75**(14):1226-7. doi: [10.1212/WNL.0b013e3181f5d507](https://doi.org/10.1212/WNL.0b013e3181f5d507). [PubMed: [20826715](https://pubmed.ncbi.nlm.nih.gov/20826715/)].
 73. Henderson EJ, Lord SR, Brodie MA, Gaunt DM, Lawrence AD, Close JC, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPOND): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016;**15**(3):249-58. doi: [10.1016/s1474-](https://doi.org/10.1016/s1474-)

- 4422(15)00389-0.
74. Mancini M, Chung K, Zajack A, Martini DN, Ramsey K, Lapidus J, et al. Effects of augmenting cholinergic neurotransmission on balance in Parkinson's disease. *Parkinsonism Relat Disord*. 2019;**69**:40–7. doi: [10.1016/j.parkreldis.2019.10.022](https://doi.org/10.1016/j.parkreldis.2019.10.022). [PubMed: [31675664](https://pubmed.ncbi.nlm.nih.gov/31675664/)].
 75. Kaushik V, Smith ST, Mikobi E, Raji MA. Acetylcholinesterase Inhibitors: Beneficial Effects on Comorbidities in Patients with Alzheimer's Disease. *Am J Alzheimers Dis Other Dement*. 2018;**33**(2):73–85. doi: [10.1177/1533317517734352](https://doi.org/10.1177/1533317517734352). [PubMed: [28974110](https://pubmed.ncbi.nlm.nih.gov/28974110/)].
 76. Urrestarazu E, Iriarte J. Clinical management of sleep disturbances in Alzheimer's disease: current and emerging strategies. *Nat Sci Sleep*. 2016;**8**:21–33. doi: [10.2147/NSS.S76706](https://doi.org/10.2147/NSS.S76706). [PubMed: [26834500](https://pubmed.ncbi.nlm.nih.gov/26834500/)]. [PubMed Central: [PMC4716729](https://pubmed.ncbi.nlm.nih.gov/PMC4716729/)].
 77. Kazui H, Adachi H, Kanemoto H, Yoshiyama K, Wada T, Tokumasu Nomura K, et al. Effects of donepezil on sleep disturbances in patients with dementia with Lewy bodies: An open-label study with actigraphy. *Psychiatry Res*. 2017;**251**:312–8. doi: [10.1016/j.psychres.2017.02.039](https://doi.org/10.1016/j.psychres.2017.02.039). [PubMed: [28236784](https://pubmed.ncbi.nlm.nih.gov/28236784/)].
 78. Buckley AW, Salloway K, Rodriguez AJ, Jennison K, Wingert K, Buckley J, et al. An open label trial of donepezil for enhancement of rapid eye movement sleep in young children with autism spectrum disorders. *J Child Adolesc Psychopharmacol*. 2011;**21**(4):353–7. doi: [10.1089/cap.2010.0121](https://doi.org/10.1089/cap.2010.0121). [PubMed: [21851192](https://pubmed.ncbi.nlm.nih.gov/21851192/)]. [PubMed Central: [PMC3157749](https://pubmed.ncbi.nlm.nih.gov/PMC3157749/)].
 79. Hsieh CF, Tseng PT, Chen TY, Lin PY, Chen YW, Bo-Lin H, et al. The association of changes of sleep architecture related to donepezil: A systematic review and meta-analysis. *J Formos Med Assoc*. 2022;**121**(8):1466–77. doi: [10.1016/j.jfma.2021.10.013](https://doi.org/10.1016/j.jfma.2021.10.013). [PubMed: [34753629](https://pubmed.ncbi.nlm.nih.gov/34753629/)].
 80. Fitzgerald PJ, Hale PJ, Ghimire A, Watson BO. Repurposing Cholinesterase Inhibitors as Antidepressants? Dose and Stress-Sensitivity May Be Critical to Opening Possibilities. *Front Behav Neurosci*. 2021;**14**:620119. doi: [10.3389/fnbeh.2020.620119](https://doi.org/10.3389/fnbeh.2020.620119). [PubMed: [33519395](https://pubmed.ncbi.nlm.nih.gov/33519395/)]. [PubMed Central: [PMC7840590](https://pubmed.ncbi.nlm.nih.gov/PMC7840590/)].
 81. Papp M, Gruca P, Lason-Tyburkiewicz M, Willner P. Antidepressant, anxiolytic and procognitive effects of rivastigmine and donepezil in the chronic mild stress model in rats. *Psychopharmacology (Berl)*. 2016;**233**(7):1235–43. doi: [10.1007/s00213-016-4206-0](https://doi.org/10.1007/s00213-016-4206-0). [PubMed: [26769042](https://pubmed.ncbi.nlm.nih.gov/26769042/)]. [PubMed Central: [PMC4801996](https://pubmed.ncbi.nlm.nih.gov/PMC4801996/)].
 82. Lim WP, Kwan Y, Tan PLL, Mok VWL, Lee KHJ. P-501- Use of donepezil for the treatment of depression in the absence of cognitive impairment. *Eur Psychiatry*. 2012;**27**(Suppl 1):1. doi: [10.1016/s0924-9338\(12\)74668-0](https://doi.org/10.1016/s0924-9338(12)74668-0).
 83. McDermott CL, Gray SL. Cholinesterase inhibitor adjunctive therapy for cognitive impairment and depressive symptoms in older adults with depression. *Ann Pharmacother*. 2012;**46**(4):599–605. doi: [10.1345/aph.1Q445](https://doi.org/10.1345/aph.1Q445). [PubMed: [22414791](https://pubmed.ncbi.nlm.nih.gov/22414791/)].
 84. Andreasen JT, Henningsen K, Bate S, Christiansen S, Wiborg O. Nicotine reverses anhedonic-like response and cognitive impairment in the rat chronic mild stress model of depression: comparison with sertraline. *J Psychopharmacol*. 2011;**25**(8):1134–41. doi: [10.1177/026988110391831](https://doi.org/10.1177/026988110391831). [PubMed: [21169388](https://pubmed.ncbi.nlm.nih.gov/21169388/)].
 85. Karvat G, Kimchi T. Acetylcholine elevation relieves cognitive rigidity and social deficiency in a mouse model of autism. *Neuropsychopharmacology*. 2014;**39**(4):831–40. doi: [10.1038/npp.2013.274](https://doi.org/10.1038/npp.2013.274). [PubMed: [24096295](https://pubmed.ncbi.nlm.nih.gov/24096295/)]. [PubMed Central: [PMC3924518](https://pubmed.ncbi.nlm.nih.gov/PMC3924518/)].
 86. Handen BL, Johnson CR, McAuliffe-Bellin S, Murray PJ, Hardan AY. Safety and efficacy of donepezil in children and adolescents with autism: neuropsychological measures. *J Child Adolesc Psychopharmacol*. 2011;**21**(1):43–50. doi: [10.1089/cap.2010.0024](https://doi.org/10.1089/cap.2010.0024). [PubMed: [21309696](https://pubmed.ncbi.nlm.nih.gov/21309696/)]. [PubMed Central: [PMC3037196](https://pubmed.ncbi.nlm.nih.gov/PMC3037196/)].
 87. Kim JW, Seung H, Kwon KJ, Ko MJ, Lee EJ, Oh HA, et al. Subchronic treatment of donepezil rescues impaired social, hyperactive, and stereotypic behavior in valproic acid-induced animal model of autism. *PLoS One*. 2014;**9**(8). e104927. doi: [10.1371/journal.pone.0104927](https://doi.org/10.1371/journal.pone.0104927). [PubMed: [25133713](https://pubmed.ncbi.nlm.nih.gov/25133713/)]. [PubMed Central: [PMC4136791](https://pubmed.ncbi.nlm.nih.gov/PMC4136791/)].
 88. Świerczek M, Nesterowicz K. Evoking subclinical hypomania as a potential autism treatment - a hypothesis based on an up-to-date literature review. *Med Res Arch*. 2018;**6**(1):1–18.
 89. Leung JG. Donepezil-induced mania. *Consult Pharm*. 2014;**29**(3):191–5. doi: [10.4140/TCP.n.2014.191](https://doi.org/10.4140/TCP.n.2014.191). [PubMed: [24589768](https://pubmed.ncbi.nlm.nih.gov/24589768/)].
 90. Rao V, Ovitt L, Robbins B. Donepezil induced hypomania. *J Neuropsychiatry Clin Neurosci*. 2008;**20**(1):107. doi: [10.1176/jnp.2008.20.1.107](https://doi.org/10.1176/jnp.2008.20.1.107). [PubMed: [18305295](https://pubmed.ncbi.nlm.nih.gov/18305295/)].
 91. Pompeia S, Gouveia JR, Galduroz JC. Acute mood effect of donepezil in young, healthy volunteers. *Hum Psychopharmacol*. 2013;**28**(3):263–9. doi: [10.1002/hup.2319](https://doi.org/10.1002/hup.2319). [PubMed: [23653426](https://pubmed.ncbi.nlm.nih.gov/23653426/)].
 92. Lu J, Wu W. Cholinergic modulation of the immune system - A novel therapeutic target for myocardial inflammation. *Int Immunopharmacol*. 2021;**93**:107391. doi: [10.1016/j.intimp.2021.107391](https://doi.org/10.1016/j.intimp.2021.107391). [PubMed: [33548577](https://pubmed.ncbi.nlm.nih.gov/33548577/)].
 93. Fujii T, Mashimo M, Moriwaki Y, Misawa H, Ono S, Horiguchi K, et al. Expression and Function of the Cholinergic System in Immune Cells. *Front Immunol*. 2017;**8**:1085. doi: [10.3389/fimmu.2017.01085](https://doi.org/10.3389/fimmu.2017.01085). [PubMed: [28932225](https://pubmed.ncbi.nlm.nih.gov/28932225/)]. [PubMed Central: [PMC5592202](https://pubmed.ncbi.nlm.nih.gov/PMC5592202/)].
 94. Martelli D, McKinley MJ, McAllen RM. The cholinergic anti-inflammatory pathway: a critical review. *Auton Neurosci*. 2014;**182**:65–9. doi: [10.1016/j.autneu.2013.12.007](https://doi.org/10.1016/j.autneu.2013.12.007). [PubMed: [24411268](https://pubmed.ncbi.nlm.nih.gov/24411268/)].
 95. Cox MA, Bassi C, Saunders ME, Nechanitzky R, Morgado-Palacin I, Zheng C, et al. Beyond neurotransmission: acetylcholine in immunity and inflammation. *J Intern Med*. 2020;**287**(2):120–33. doi: [10.1111/joim.13006](https://doi.org/10.1111/joim.13006). [PubMed: [31710126](https://pubmed.ncbi.nlm.nih.gov/31710126/)].
 96. Hoover DB. Cholinergic modulation of the immune system presents new approaches for treating inflammation. *Pharmacol Ther*. 2017;**179**:1–16. doi: [10.1016/j.pharmthera.2017.05.002](https://doi.org/10.1016/j.pharmthera.2017.05.002). [PubMed: [28529069](https://pubmed.ncbi.nlm.nih.gov/28529069/)]. [PubMed Central: [PMCS5651192](https://pubmed.ncbi.nlm.nih.gov/PMCS5651192/)].
 97. Hwang J, Hwang H, Lee HW, Suk K. Microglia signaling as a target of donepezil. *Neuropharmacology*. 2010;**58**(7):1122–9. doi: [10.1016/j.neuropharm.2010.02.003](https://doi.org/10.1016/j.neuropharm.2010.02.003). [PubMed: [20153342](https://pubmed.ncbi.nlm.nih.gov/20153342/)].
 98. Leszek JW, Blach-Olszewska Z, Zaczynska E, Siemieniec I. P2-205: The effect of donepezil on the reactions of the innate immune system in the peripheral blood leukocytes of healthy young blood donors. *Alzheimer's Dement*. 2009;**5**(4(S Pt 11)):P320–1. doi: [10.1016/j.jalz.2009.04.518](https://doi.org/10.1016/j.jalz.2009.04.518).
 99. Sochocka M, Zaczynska E, Leszek J, Siemieniec I, Blach-Olszewska Z. Effect of donepezil on innate antiviral immunity of human leukocytes. *J Neurol Sci*. 2008;**273**(1-2):75–80. doi: [10.1016/j.jns.2008.06.021](https://doi.org/10.1016/j.jns.2008.06.021). [PubMed: [18662817](https://pubmed.ncbi.nlm.nih.gov/18662817/)].
 100. Vela JM. Repurposing Sigma-1 Receptor Ligands for COVID-19 Therapy? *Front Pharmacol*. 2020;**11**:582310. doi: [10.3389/fphar.2020.582310](https://doi.org/10.3389/fphar.2020.582310). [PubMed: [33364957](https://pubmed.ncbi.nlm.nih.gov/33364957/)]. [PubMed Central: [PMC7751758](https://pubmed.ncbi.nlm.nih.gov/PMC7751758/)].
 101. Hashimoto K. Repurposing of CNS drugs to treat COVID-19 infection: targeting the sigma-1 receptor. *Eur Arch Psychiatry Clin Neurosci*. 2021;**271**(2):249–58. doi: [10.1007/s00406-020-02131-x](https://doi.org/10.1007/s00406-020-02131-x). [PubMed: [33403480](https://pubmed.ncbi.nlm.nih.gov/33403480/)]. [PubMed Central: [PMC7785036](https://pubmed.ncbi.nlm.nih.gov/PMC7785036/)].
 102. Rahman MA, Islam K, Rahman S, Alamin M. Neurobiochemical Cross-talk Between COVID-19 and Alzheimer's Disease. *Mol Neurobiol*. 2021;**58**(3):1017–23. doi: [10.1007/s12035-020-02177-w](https://doi.org/10.1007/s12035-020-02177-w). [PubMed: [33078369](https://pubmed.ncbi.nlm.nih.gov/33078369/)]. [PubMed Central: [PMC7571527](https://pubmed.ncbi.nlm.nih.gov/PMC7571527/)].