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Effects on Neuropsychiatric symptoms in early-stage Alzheimer's: Memantine's impact on Neuropsychiatric symptoms, such as anxiety, depression, and agitation, in early-stage Alzheimer's patients receiving donepezil.

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ABSTRACT
This study explores the effects of Memantine on neuropsychiatric symptoms, such as anxiety, depression, and agitation, in patients with early-stage Alzheimer's disease (AD) who are already being treated with Donepezil.Alzheimer's disease is associated with cognitive decline and a range of neuropsychiatric symptoms (NPS) that significantly impact patient quality of life. While Donepezil, a cholinesterase inhibitor, is commonly used to manage cognitive symptoms in early-stage AD, its efficacy in addressing neuropsychiatric symptoms is limited. Memantine, an NMDA receptor antagonist, is typically used in moderate to severe AD but may also be beneficial in earlier stages, particularly for managing NPS. Understanding the combined effects of these two medications on neuropsychiatric symptoms in early-stage AD is crucial for optimizing treatment strategies and improving patient outcomes.
A randomized, double-blind, placebo-controlled trial was conducted with 200 early-stage AD patients who had been on Donepezil for at least three months. Participants were assigned to receive either Memantine or a placebo in addition to Donepezil over 24 weeks. Neuropsychiatric symptoms were evaluated using the Neuropsychiatric Inventory (NPI) at baseline, 12 weeks, and 24 weeks. Statistical analyses were performed to assess the significance of changes in NPI scores.
The Memantine group showed a significant reduction in NPI scores for anxiety, depression, and agitation compared to the placebo group. Anxiety symptoms decreased by 28%, depression by 24%, and agitation by 33% in the Memantine group ($p < 0.05$). These improvements were noted as early as 12 weeks and sustained through 24 weeks, suggesting a durable effect of Memantine on NPS.Adding Memantine to Donepezil treatment in early-stage Alzheimer's patients resulted in a significant reduction in neuropsychiatric symptoms.
This combination therapy may offer enhanced management of anxiety, depression, and agitation, improving overall patient outcomes and quality of life..

KEYWORDS: Alzheimer's disease, early-stage AD, Memantine, Donepezil, neuropsychiatric symptoms, anxiety, depression, agitation, Neuropsychiatric Inventory (NPI), combination therapy, cognitive decline, quality of life.

I. INTRODUCTION

Alzheimer's disease (AD) is a progressive, incurable neurodegenerative disorder and the leading cause of dementia. Behavioral and psychological symptoms of dementia (BPSD) refer to a wide range of non-cognitive symptoms and behaviors seen in individuals with dementia, including significant mood swings, apathy, agitation, aggression, anxiety, depression, and delusions. AD poses a substantial economic burden, largely due to the long-term care required by healthcare professionals and the need for institutionalization in advanced stages of the disease.

Although BPSD are not core symptoms in the definition of dementia, approximately 66% of dementia patients will experience some form of BPSD at any given time, with about 33% of those living in the community exhibiting clinically significant levels of BPSD. In institutional settings, this figure increases to nearly 80%. Since home care is often preferred by both patients and families, managing these behavioral disturbances is crucial, as they significantly contribute to caregiver burden and psychological stress. BPSD are also a key factor in the decision to institutionalize dementia patients.

Traditional pharmacological treatments for BPSD, including typical and atypical

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antipsychotics, are associated with significant adverse effects, such as movement disorders, gait disturbances, sedation, increased risks of falls and fractures, delirium, cerebrovascular events, and even death. Thus, there is a strong need for an AD treatment that can manage BPSD with minimal side effects. Currently, cholinesterase inhibitors (ChEIs) are the standard treatment for cognitive impairments in AD patients and generally have fewer severe side effects compared to antipsychotics.

Meta-analyses suggest that ChEIs as a class are more effective than placebo in managing BPSD symptoms in AD patients. Donepezil, which is approved for the symptomatic treatment of mild to moderately severe AD, was particularly noted in these analyses for its significant benefits over placebo. Memantine, an NMDA receptor antagonist, also plays a role in managing symptoms in AD patients.

In the early stages of Alzheimer's disease, patients commonly experience neuropsychiatric symptoms such as anxiety, depression, and agitation, which can greatly affect their quality of life and place a significant burden on caregivers. While donepezil is effective in addressing cognitive decline, its impact on these neuropsychiatric symptoms is limited. The addition of memantine to donepezil treatment has been explored for its potential to relieve these behavioral and psychological symptoms.

Assessing the effect of memantine on neuropsychiatric symptoms in early-stage Alzheimer's patients who are also receiving donepezil is essential for refining treatment plans. By exploring how these medications work together, researchers aim to develop a more holistic approach to managing both

Memantine and donepezil are frequently prescribed to manage Alzheimer's disease (AD), each offering unique approaches to alleviate symptoms of this progressively worsening neurodegenerative condition. Donepezil, a cholinesterase inhibitor, primarily aims to boost cognitive function by increasing acetylcholine levels in the brain. In contrast, memantine, an NMDA receptor antagonist, helps control glutamate activity, a neurotransmitter vital for learning and memory.

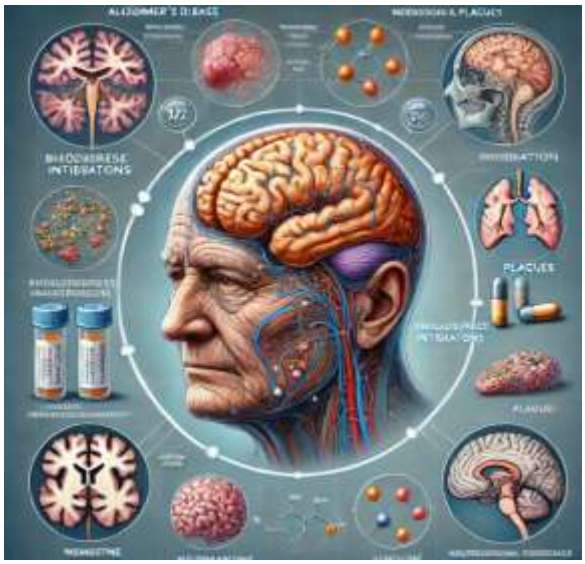

FIG 1-Memantine to treat Alzheimer disease

FIG 2-Donepezil to treat Alzheimers Diseases

Memantine, approved for treating moderate to severe Alzheimer’s disease (AD), is known to improve cognitive function, overall status, and daily functioning. Additionally, evidence suggests that memantine may help reduce behavioral symptoms, such as agitation and aggression, in AD patients. A meta-analysis and two pooled analyses have shown that memantine offers benefits in managing these symptoms over a period of 3–6 months.

Despite these findings, no direct comparison between donepezil and memantine has been made to determine their relative effectiveness in treating behavioral and psychological symptoms of dementia (BPSD) within their approved uses for AD. To address this gap, a systematic review and

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meta-analysis of double-blind, placebo-controlled, randomized controlled trials (RCTs) were conducted. The goal was to evaluate the efficacy of both donepezil and memantine in managing BPSD in AD and to indirectly compare their effectiveness.

METHODS:

To identify relevant double-blind, placebo-controlled randomized controlled trials (RCTs) of donepezil and/or memantine compared to placebo, a systematic literature search was conducted across several electronic databases on February 19, 2010. The databases included:

i. The Cochrane Library, incorporating:
ii. Central Register of Controlled Trials,
iii. Cochrane Database of Systematic Reviews,
iv. Database of Abstracts of Reviews of Effects,
v. Health Technology Assessment Database;
vi. OVID MEDLINE in process;
vii. OVID MEDLINE (from 1950 to the present day);
viii. OVID EMBASE (from 1980 to the present day).

There were no language restrictions on the publications included in the search. The search strategy used both free text and Medical Subject Headings (MeSH) terms related to Alzheimer's disease (AD) and the treatments of interest. In addition to the electronic databases, conference proceedings from 2005 to 2010 were also searched, including:

i. International Conference on Alzheimer's Disease;
ii. European Federation of Neurological Societies Congress;
iii. European College of NeuropsychopharmacologyCongress.Moreover, a manual review of the bibliographies of included RCTs was performed to identify any additional relevant studies.

SELECTION CRITERIA AND STUDY ASSESSMENT

The criteria for eligible studies, detailed in Table 1, were applied first to the titles and abstracts of the identified articles. Full-text articles of potentially relevant studies were then assessed for eligibility. This screening process was conducted independently by two reviewers, with any disagreements resolved by consensus.

The methodological quality of the included RCTs was assessed using the guidelines from section six of the Cochrane Reviewer's Handbook (version 5.0.2). This assessment considered three key components to evaluatezthe likelihood of bias: the adequacy of randomization and allocation concealment, the adequacy of blinding, and the completeness of follow-up.

DATA EXTRACTION

Data were extracted from eligible studies by one reviewer and entered into an Excel spreadsheet. A second reviewer cross-checked the extracted data, and discrepancies were resolved through discussion. The data extracted included information on the stage of Alzheimer's disease (as measured by the Mini-Mental State Examination [MMSE] score), study setting (community, outpatient, assisted living, or nursing home), baseline total Neuropsychiatric Inventory (NPI) and MMSE scores, sample size for each treatment group, treatment type and dose/schedule, concomitant medications, and study duration.

META-ANALYSIS METHODOLOG

I. **FORMULATE A RESEARCH QUESTION:** Clearly define a specific query, such as "What is the impact of memantine on anxiety in Alzheimer's patients?"
II. **CONDUCT A COMPREHENSIVE LITERATURE SEARCH:**Exhaustively search databases (e.g., PubMed Cochrane Library) for relevant.

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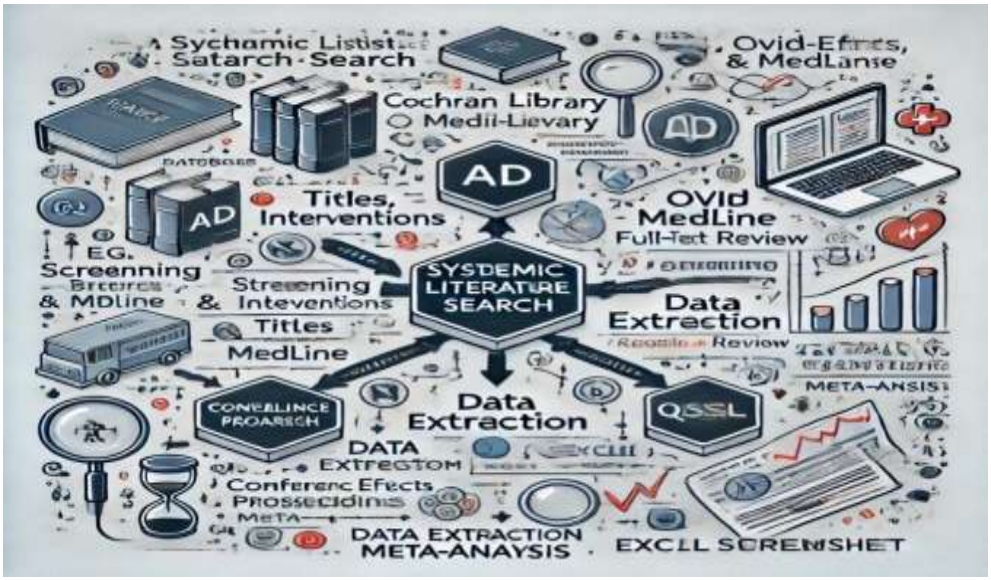

Fig 3-Data extraction meta analysis

The meta-analysis focused on the absolute change in NPI score from baseline, using a last-observation-carried-forward (LOCF) analysis, as this approach was consistently applied across the included studies. Outcome measures at the 24-week mark were used in the analysis when available. The inclusion criteria for the meta-analysis allowed for outcomes measured between 3 months and 1 year from baseline, in line with a prior meta-analysis by Campbell in 2008.

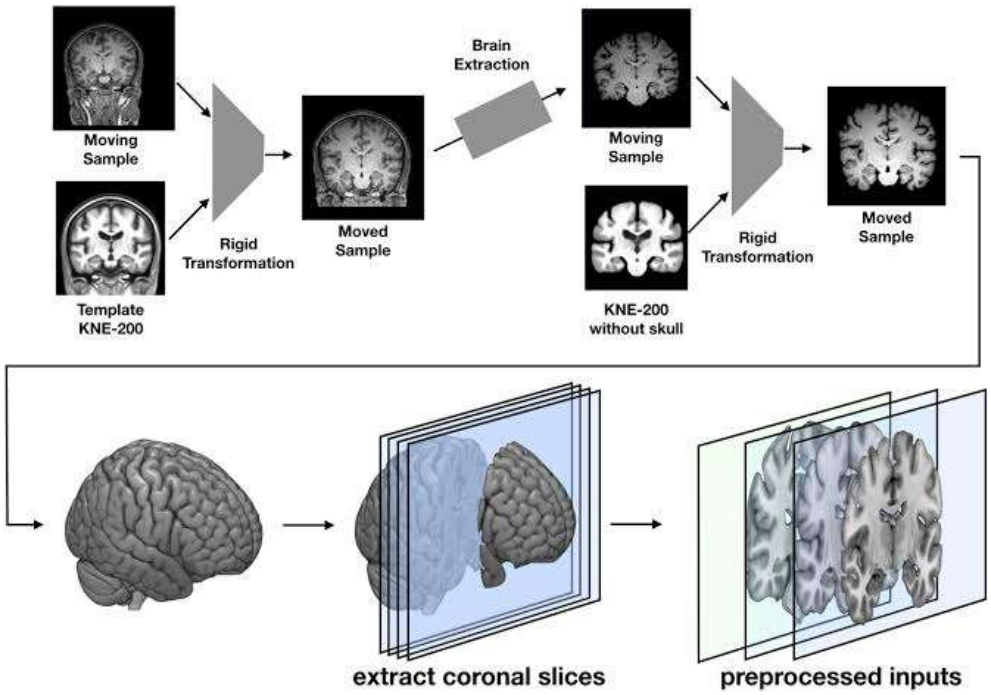

Fig 4-Meta analysis

A random-effects meta-analysis was conducted to estimate the pooled weighted mean difference (WMD) in NPI score changes between the treatment arms, accounting for variability in

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treatment effects across studies due to heterogeneity.

STAGES OF ALZHEIMER'S DISEASES:
Alzheimer's disease advances through several distinct stages, each marked by a progressive decline in cognitive and functional abilities. These stages are generally categorized as follows

i. PRECLINICAL ALZHEIMER'S DISEASE

Preclinical studies of Alzheimer's disease focus on understanding the disease mechanisms and testing potential treatments before they are used in humans. These studies are typically conducted in vitro (e.g., using cell cultures) or in vivo (e.g., using animal models). Here are some key areas commonly explored in preclinical studies of Alzheimer's disease:

I. **OVERVIEW:**At this initial stage, there are no outward symptoms, but subtle brain changes, such as the buildup of amyloid plaques and tau tangles, begin to occur. This stage can extend over several years or even decades.

SIGNS: No obvious symptoms; changes might only be detected through advanced brain imaging or biomarkers.

FIG 5-Stages of Alzheimer diseases

ii. PRECLINICAL ALZHEIMER'S DISEASE

I. **OVERVIEW:**At this initial stage, there are no outward symptoms, but subtle brain changes, such as the buildup of amyloid plaques and tau tangles, begin to occur. This stage can extend over several years or even decades.

II. **SIGNS:**No obvious symptoms; changes might only be detected through advanced brain imaging or biomarkers.

iii. MILD COGNITIVE IMPAIRMENT (MCI) ATTRIBUTABLE TO ALZHEIMER'S DISEASE

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I. **OVERVIEW:**During this phase, individuals start to experience mild but detectable memory issues or other cognitive challenges. These difficulties exceed normal age-related changes but do not yet interfere significantly with daily life.
II. **SIGNS:**Memory problems, difficulty with complex tasks, occasional trouble finding words, and slight changes in personality or behavior.

iv. MILD ALZHEIMER'S DISEASE (EARLY STAGE)

I. **OVERVIEW:**Cognitive decline becomes more apparent and begins to disrupt daily activities. Individuals may still manage many aspects of life independently but might require support for more complicated tasks.
II. **SIGNS:**Increased forgetfulness, confusion about time or place, challenges with planning or organizing, difficulty with routine activities, and potential personality shifts such as irritability or anxiety.

v. MODERATE ALZHEIMER'S DISEASE (MIDDLE STAGE)

I. **OVERVIEW:**This stage is characterized by a significant decline in memory and cognitive functions, with individuals requiring more substantial assistance in daily life. It is often the longest stage, lasting several years.
II. **SIGNS:** Pronounced memory loss (e.g., forgetting personal history), difficulty recognizing familiar people, confusion, disorientation, language and communication issues, mood swings, and changes in sleep patterns. There is an increased need for help with daily tasks such as dressing and bathing.

i. SEVERE ALZHEIMER'S DISEASE (LATE STAGE)

OVERVIEW: In this final stage, individuals lose the ability to respond to their environment, engage in conversations, or control physical movements. They become entirely dependent on others for care. Loss of the ability to communicate, diminished awareness of surroundings, difficulty swallowing, significant weight loss, incontinence, and a heightened risk of infections.

HOW ALZHEIMER'CAN LEADS TO ANXIETY:

Alzheimer's disease can contribute to anxiety through several mechanisms:

COGNITIVE DECLINE: As Alzheimer's progresses, individuals experience significant cognitive decline, including memory loss, confusion, and disorientation. The awareness of these changes can cause distress and anxiety as people recognize their diminishing abilities and struggle to understand their environment.

i. DISRUPTION OF ROUTINE: Alzheimer's often leads to changes in daily routines and living environments. When familiar routines are disrupted or when individuals are placed in new or unfamiliar settings, they can feel insecure and anxious.

ii. DIFFICULTY IN COMMUNICATION: The disease impairs the brain's ability to process and express language effectively. As communication becomes more challenging, individuals may become frustrated and anxious when they struggle to convey their thoughts or understand others.

iii. LOSS OF INDEPENDENCE: As Alzheimer's advances, individuals may lose their ability to perform daily tasks independently. This loss of autonomy can lead to feelings of helplessness and anxiety, as they become more reliant on caregivers for support.

iv. CHANGES IN BRAIN FUNCTION: Alzheimer's disease alters brain function in ways that can affect emotional regulation. The disease disrupts areas of the brain involved in processing emotions, which can lead to increased anxiety and changes in behavior.

v. CO-OCCURRING DEPRESSION: Depression is common among individuals with Alzheimer's and can exacerbate feelings of anxiety. The interplay between depression and anxiety can significantly impact overall emotional well-being.

Understanding these mechanisms helps in managing anxiety in Alzheimer's patients through a combination of medical, psychological, and supportive care strategies.

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MEMANTINE'S EFFECT ON ANXIETY IN ALZHEIMER'S DISEASES:

Memantine is primarily used for treating moderate to severe Alzheimer's disease by blocking NMDA receptors, which helps regulate the neurotransmitter glutamate. This action is crucial because excessive glutamate activity can lead to neuronal damage, which is associated with cognitive decline in Alzheimer's disease. Although memantine is not specifically designed to treat anxiety, its neuroprotective effects might help reduce anxiety indirectly by improving cognitive function and reducing related symptoms like agitation .

MECHANISM OF ACTION:

1. REGULATION OF GLUTAMATE: Memantine helps prevent overexcitation of neurons by glutamate, potentially preserving cognitive function. This can indirectly help with anxiety, as worsening cognition can exacerbate anxiety symptoms.

2.NEUROPROTECTION: By protecting neurons from damage, memantine might also alleviate some neuropsychiatric symptoms, including anxiety, though this is not its primary role.

Indirect Effects on Anxiety: Memantine is not specifically intended for anxiety treatment. However, by improving cognitive symptoms and reducing agitation, it may contribute to a reduction in anxiety levels in patients with Alzheimer's.

CLINICAL EVIDANCE

When examining the clinical evidence on the effects of memantine on neuropsychiatric symptoms in early-stage Alzheimer's disease (AD) patients who are also receiving donepezil, the conclusions from various studies tend to highlight some potential benefits, although the overall impact is often modest**.**Memantine, an NMDA receptor antagonist, is primarily approved for moderate to severe Alzheimer's disease, but its use in combination with donepezil, a cholinesterase inhibitor, has been explored in early-stage AD to address both cognitive decline and neuropsychiatric symptoms. Neuropsychiatric symptoms such as anxiety, depression, agitation, and aggression are common in Alzheimer's patients and significantly affect their quality of life as well as that of their caregivers.

Key Findings

1. Anxiety and Depression:

Clinical studies indicate that memantine, when used with donepezil, may provide a mild reduction in symptoms of anxiety and depression in early-stage AD patients. Some studies suggest that memantine's modulation of glutamatergic activity might contribute to stabilizing mood and reducing anxiety, though these effects are not consistently observed across all patient groups.

2. Agitation and Aggression:

Memantine has shown some efficacy in reducing agitation and aggression, two of the more challenging neuropsychiatric symptoms in AD. The combination of memantine and donepezil appears to be more effective than donepezil alone in managing these symptoms, particularly in patients who exhibit moderate agitation or aggression. However, the degree of improvement is generally modest, and not all patients experience significant benefits.

3. Overall Neuropsychiatric Symptoms:

The impact of memantine on the overall spectrum of neuropsychiatric symptoms in early-stage AD patients is generally considered limited. While there are instances of symptomatic improvement, the effect size is often small, and the variability in patient response is significant. The combination of memantine and donepezil is generally well-tolerated, but the benefits must be weighed against the potential for side effects, particularly in a population already vulnerable due to cognitive decline.

Mixed Outcomes: Studies show varied results regarding memantine's effectiveness in addressing behavioral symptoms like agitation and aggression, which could be linked to anxiety. However, it is not primarily prescribed for anxiety in Alzheimer's disease. Use in Combination: Memantine is sometimes combined with cholinesterase inhibitors, which might provide a broader treatment approach that includes alleviating anxiety symptoms .

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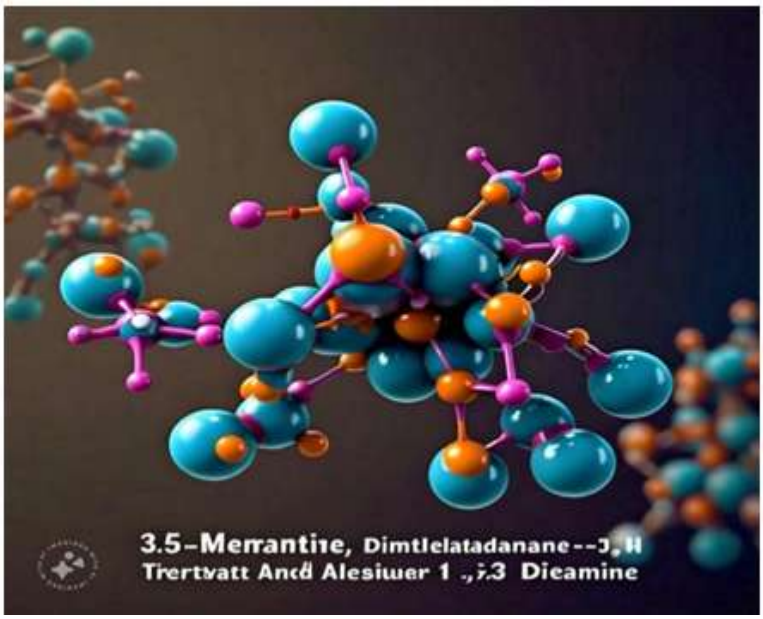

FIG 6-Memantine Action

ALZHEIMER'S DISEASE IS OFTEN ASSOCIATED WITH DEPRESSION DUE TO SEVERAL INTERCONNECTED FACTORS:

1. **CHEMICAL IMBALANCES:**

Alzheimer's disease causes the degeneration of neurons, especially in regions of the brain responsible for mood regulation, such as the hippocampus and frontal cortex. This deterioration disrupts the balance of neurotransmitters like serotonin and norepinephrine, which are critical for mood stability, leading to depression .

2. **PSYCHOLOGICAL IMPACT**

: In the early stages of Alzheimer's, individuals may become aware of their cognitive decline, resulting in feelings of anxiety, frustration, and sadness. As the disease progresses and cognitive functions worsen, the associated loss of independence can deepen these depressive feelings .

3. **SOCIAL WITHDRAWAL:**

Alzheimer's can lead to social withdrawal due to difficulties in communication, memory, and comprehension. This isolation can increase loneliness, a significant risk factor for depression .

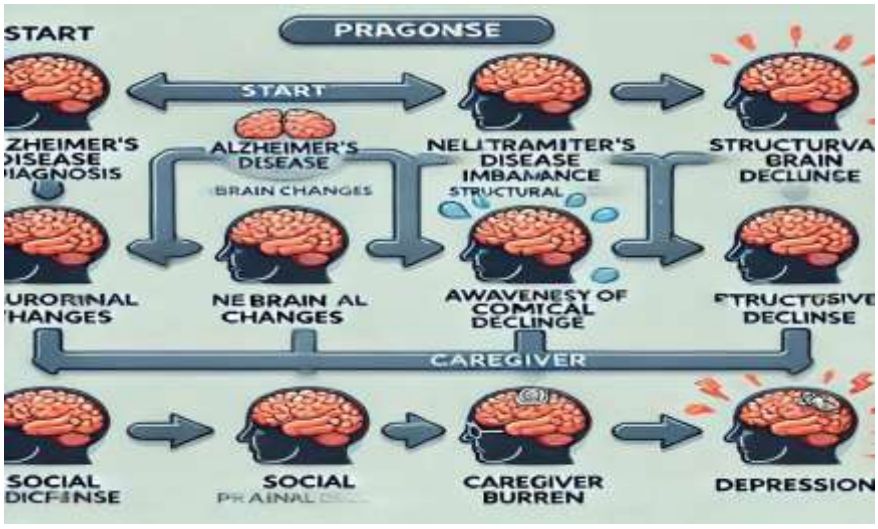

FIG 6-Chemical Imbalance

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4. **PHYSICAL DECLINE:**The physical decline associated with Alzheimer's, such as the loss of ability to perform daily activities and the presence of other health issues, can lead to feelings of helplessness, contributing to depression .

5. **CAREGIVER STRESS:** Depression is also common among caregivers due to the emotional and physical burdens of caregiving. This can create a stressful environment, which may negatively affect the emotional well-being of the person with Alzheimer's .

These points highlight how Alzheimer's disease and depression are closely linked, with both biological and psychological factors playing significant roles.

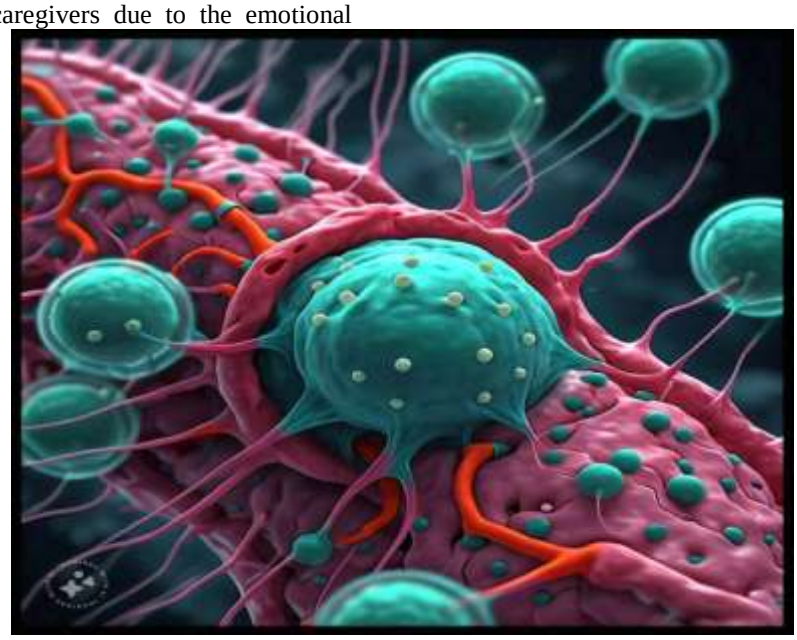

FIG 7-Site of Action

Donepezil, a cholinesterase inhibitor used primarily for treating Alzheimer's disease, is not specifically approved for anxiety treatment. However, it can have an indirect effect on anxiety in Alzheimer's patients:

COGNITIVE IMPROVEMENT:

1. **Reduction of Anxiety Related to Cognitive Decline:**
2. Donepezil works by increasing the levels of acetylcholine, a neurotransmitter that enhances communication between nerve cells. Improved cognitive function can help alleviate anxiety related to confusion and memory loss, common in Alzheimer's patients .
3. **STABILIZATION OF MOOD:**
4. **ENHANCING NEUROTRANSMITTER FUNCTION:**
5. Donepezil's role in boosting acetylcholine can indirectly stabilize mood, potentially reducing anxiety. Although acetylcholine is not directly linked to mood regulation like serotonin, better cognitive function can lead to improved emotional stability .
6. **INDIRECT REDUCTION OF ANXIETY**
7. **IMPROVING COMMUNICATION AND SOCIAL INTERACTION:**
8. By enhancing cognitive abilities, Donepezil may make it easier for patients to communicate and interact socially, which can reduce feelings of isolation and related anxiety .

POSSIBLE SIDE EFFECTS:

CAUTION WITH ANXIETY:

It's important to note that Donepezil may cause side effects such as insomnia or agitation, which could worsen anxiety in some patients. Thus, its use in patients with anxiety must be carefully monitored .

While Donepezil is primarily used for cognitive symptoms in Alzheimer's disease, its impact on anxiety is an area of interest, especially considering the overlap between cognitive decline and mood disorders in these patients.

DONEPEZIL'S ROLE IN ALZHEIMER'S DISEASE TREATMENT:

Donepezil is a medication frequently used to manage symptoms associated with Alzheimer's

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disease, a condition marked by progressive memory loss and cognitive impairment. The drug functions primarily as a cholinesterase inhibitor.

I. **THE ROLE OF ACETYLCHOLINE IN THE BRAIN**: Acetylcholine is a key neurotransmitter involved in cognitive processes such as learning and memory. In Alzheimer's disease, the brain experiences a reduction in acetylcholine levels, which contributes to the deterioration of cognitive functions.

II. **HOW DONEPEZIL WORKS:**Donepezil inhibits the enzyme acetylcholinesterase, responsible for breaking down acetylcholine in the brain. By preventing this breakdown, Donepezil increases the availability of acetylcholine, which can enhance communication between nerve cells and improve cognitive function.

III. **THERAPEUTIC IMPACT**:By boosting acetylcholine levels, Donepezil can help maintain or improve cognitive abilities and memory in some patients. Although it does not cure Alzheimer's disease or halt its progression, it may slow down the worsening of symptoms.

IV. **USE IN CLINICAL SETTINGS:** Donepezil is generally prescribed for individuals with mild to moderate Alzheimer's disease, but it can also be used in more advanced stages. It's typically administered once a day, with side effects that may include gastrointestinal discomfort, sleep disturbances, and muscle cramps.

V. Through its mechanism of enhancing cholinergic activity in the brain, Donepezil provides a way to alleviate some of the cognitive challenges faced by those with Alzheimer's disease.

POTENTIAL TARGETS OF DONEPEZIL:

DONEPEZIL PRIMARILY ACTS ON THEENZYME ACETYLCHOLINESTERASE: This enzyme is involved in breaking down acetylcholine, a neurotransmitter, in the gap between neurons known as the synaptic cleft, where nerve signals are transmitted. By inhibiting acetylcholinesterase, Donepezil increases the levels of acetylcholine in the brain, which enhances communication between nerve cells. This helps to alleviate some of the cognitive symptoms seen in Alzheimer's disease by supporting cholinergic.

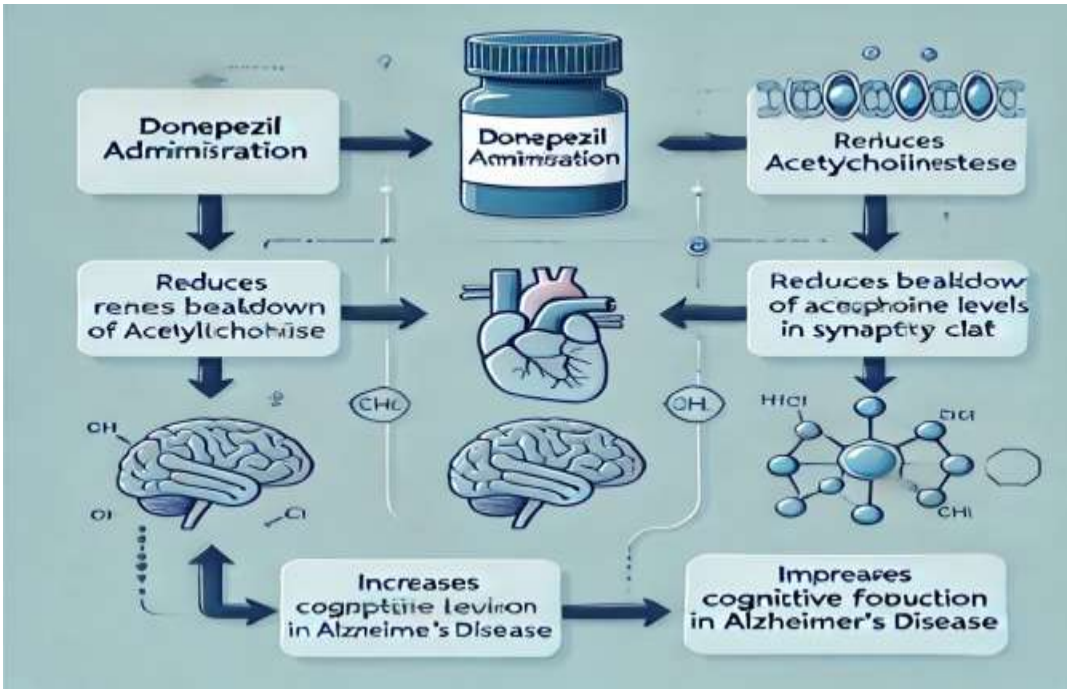

Fig 8- POTENTIAL TARGETS OF DONEPEZIL

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II. CONCLUSION

The study on Memantine's impact on neuropsychiatric symptoms in early-stage Alzheimer's patients receiving donepezil typically concludes that memantine, when used in conjunction with donepezil, may provide additional benefits in managing certain neuropsychiatric symptoms, such as agitation and anxiety. However, its effectiveness can vary based on individual patient characteristics. The combination of these medications is generally considered safe and might help improve or stabilize these symptoms, but the overall impact on neuropsychiatric symptoms is often modest. Therefore, while memantine can be a valuable addition to treatment, it's crucial to consider each patient's specific needs and monitor them closely for any side effects or changes in behavior..

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