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Health Implications and Side Effects of Donepezil and Memantine Co-Therapy: A Review.

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KEYWORDS

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ABSTRACT:

Donepezil and Memantine are commonly utilized in tandem as a treatment for Alzheimer's disease. Alzheimer's disease is a degenerative brain disorder that progressively leads to memory impairment, cognitive deterioration, and changes in behavior. Donepezil and Memantine are two of the most frequently prescribed medications for alleviating symptoms of Alzheimer's disease. Other drugs approved by the FDA to subdue Alzheimer's symptoms are Rivastigmine and Galantamine. Donepezil acts as a reversible acetylcholinesterase inhibitor, which improves cholinergic transmission by raising acetylcholine levels within the brain. Memantine functions as an NMDA receptor antagonist, which mitigates excitotoxicity resulting from excessive glutamate activity, thus safeguarding neurons from harm. Although the clinical effectiveness of these medications is well established, their side effects and toxicological profiles present notable concerns regarding their safety. Therefore, this review intends to emphasize the health implications and side effects associated with both of these medications. It also examines the chemical characteristics, pharmacological mechanisms, drug interactions and risk summary in particular populations.

1. INTRODUCTION:

In order to create new, more selective, and effective medications that can address the emergence of drug resistance, there has been an increasing interest in the multi-target and polypharmacologic approach to treat a variety of diseases, including Alzheimer's disease (AD), in recent years [1,2].

In clinical practice, combining two or more medications has demonstrated encouraging therapeutic results. But, especially in susceptible groups like the elderly or people with comorbidities, this strategy also raises questions about possible side effects, drug-drug interactions, and the possibility of irreversible consequences, including increased toxicity, cognitive impairment, or even death [3].

One such instance of a polypharmacologic strategy is the combination therapy of donepezil with memantine. Despite the combination's apparent clinical efficacy in reducing Alzheimer's symptoms, its concerning side effects should not be disregarded.

It is challenging to completely understand the mechanisms underlying the negative effects due to the inherent limitations of clinical trials, including the rigorous study design, stringent enrollment requirements, relatively small sample sizes, short

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follow-up periods, and the fact that dementia typically lasts for several years.

These factors make it challenging to explain the side effects (AEs) of donepezil and memantine for AD in the real world [4].

This review focuses on highlighting the drug donepezil and memantine and the side effects which has been observed due to this combination therapy.

2. CHEMICAL PROPERTIES:

Donepezil-

- The chemical name for Donepezil is (2-[(1-benzylpiperidin-4-yl) methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one) [5].
- The chemical formula is $C_{24}H_{29}NO_3$, while the molecular weight is 379.492 g/mol [5].
- Donepezil is a white crystalline powder [5].
- The Pka value is 8.9 (basic) [6].
- The melting point of Donepezil Hydrochloride is in the range of 218-220℃ [7].
- Donepezil is freely soluble in water and in chloroform, sparingly soluble in glacial acetic acid and in ethanol, slightly soluble in acetonitrile, very slightly soluble in ethyl acetate, and insoluble in n-hexane [5].

Memantine-

- The chemical name for Memantine is 3,5-dimethyl-1-aminoadamantane [8].
- The chemical formula is $C_{12}H_{21}N$, while the molecular weight is 179.3 g/mol [8].
- Memantine is a delicate white to off- white powder [8].
- The Pka value is 10.3 (basic) [9].
- The melting point of Memantine Hydrochloride is 297.16 ℃ [10].
- It is highly soluble in Dimethyl Sulfoxide and readily soluble in Water [11].

3. MECHANISM OF ACTION:

Donepezil-

- Current theories regarding the development of cognitive signs and symptoms in Alzheimer's disease suggest that some of these issues may be due to a lack of cholinergic neurotransmission.
- Donepezil is believed to work therapeutically by improving cholinergic function. This is achieved by raising the levels of acetylcholine in the central nervous system through the reversible inhibition of its breakdown by acetylcholinesterase [12].

Memantine-

- The ongoing activation of NMDA receptors in the central nervous system by glutamate, an excitatory amino acid, is thought to play a role in the symptoms associated with Alzheimer's disease.
- Memantine is believed to have a therapeutic effect due to its function as a low to moderate affinity uncompetitive antagonist of NMDA receptors, preferentially binding to the cation channels that are activated by NMDA receptors [13].

4. WARNINGS/ PRECAUTIONS:

- It has been noted that people who have never had cardiac problems before may develop Bradycardia or Heart Block as a result of combined medication. Additionally, it has been shown that the combination may cause gastrointestinal bleeding and ulcers by increasing the gastric acid output as a result of enhanced cholinergic activity. In patients with a history of Asthma or COPD, it may show negative consequences. The most frequent adverse effects are vomiting, nausea, and diarrhea [14].

5. RISK SUMMARY IN SPECIAL CASES:

a.) PEDIATRIC USE:

The combination has not been tested in children under the age of six or those over the age of twelve, and it did not show any effectiveness in two-week controlled clinical

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trials of children with autism spectrum disorder ages 6 to 12 [14].

b.) LACTATING MOTHERS:

Memantine and donepezil's presence in human milk, their effects on breastfed infants, and their metabolites' impacts on milk production are all unknown [14].

c.) PREGNANT WOMEN:

Although there is insufficient information on the developmental risk of donepezil and memantine use in pregnant women, rats given memantine/donepezil during pregnancy at doses linked to low maternal toxicity showed negative developmental effects in their offspring, including mortality, decreased body weight, and skeletal ossification. However, these dosages were greater than those administered to humans [14].

6. DRUG INTERACTIONS:

a.) Effect of other drugs on donepezil metabolism:

CYP3A4 and CYP2D6 inhibitors (like ketoconazole) block donepezil metabolism in vitro; it is unknown if quinidine has a clinical effect. CYP3A4 inducers (like phenytoin, carbamazepine, dexamethasone, rifampicin, and phenobarbital) may speed up donepezil's excretion [14].

b.) Effect of NMDA Antagonists:

Memantine should be used cautiously because its combination with other NMDA antagonists, such as amantadine, ketamine, and dextromethorphan, has not been thoroughly studied [14].

7. MEMANTINE AND DONEPEZIL COMBINATION MEDICATION ADVERSE EVENT PROFILE:

- The FAERS database, which includes adverse event reports filed by patients, manufacturers, and healthcare professionals, were studied by researchers in their investigation. The reports in the database span the years 2004 through 2023.
- The study identifies new possible concerns in addition to highlighting the information already known. The following were the side effects of the combo therapy that were observe: [15]

a.) NERVOUS SYSTEM DISORDERS:

- This includes patient suffering from vertigo, tremor, syncope, lethargy, loss of consciousness, dyskinesia, hypersomnia, speech difficulty, encephalopathy, pleurothotonus, dementia, sedation, epilepsy, facial spasms, drooling, psychomotor hyperactivity, and depression [15]

b.) PSYCHIATRIC DISORDERS:

- This includes agitation, aggression, hallucinations, abnormal behavior, restlessness, nightmares, irritability, staring, and sleep talking, as well as confusion [15]

c.) CARDIAC DISORDERS:

- This includes Myocardial infarction, Atrial fibrillation, Cardiac Arrest, Bradycardia, and Cardiac Failure [16].

d.) METABOLISM AND NUTRITION DISORDERS:

- This includes Diet rejection, polydipsia, hypophagia, and hypernatraemia [15]

e.) GENERAL DISORDERS:

- This includes- Screaming, Foaming at mouth, Sluggishness [15]

f.) INFECTIONS AND INFESTATIONS:

- This includes Gastrointestinal infection. Urosepsis [15]

g.) RENAL AND URINARY DISORDERS:

- This includes- Urinary incontinence, Ketonuria (ketone bodies in urine), Hydronephrosis (swollen kidneys) [15]

h.) GASTRO-INTESTINAL DISORDERS:

- Constipation, Salivary Hypersecretion, Faecaloma (hard, calcified accumulated faeces), diarrhea, vomiting, abdominal pain.[15, 17].

i.) **VASCULAR DISORDERS:** Thrombophlebitis (blood clot in the veins) [15]

j.) SKIN AND SUBCUTANEOUS DISORDERS:

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- This includes Skin Oedema, Yellow Skin, Decubitus Ulcer, and Purpuric rash [15, 18]

k.) MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS:

- This includes Rhabdomylosis, a condition wherein damaged skeletal muscle tissue breaks down, releasing protein myoglobin into the bloodstream, myoclonus, and torticollis/ twisted neck [15, 19]

l.) **EYE DISORDERS:** constricted/ shrunken pupil [15]

m.) REPRODUCTIVE DISORDERS:

- Enlargement of the prostate gland/ Benign prostatic hyperplasia [15]

n.) ENDOCRINE DISORDERS:

- This includes inappropriate antidiuretic hormone secretion [15]

8. CONCLUSION:

In summary, although the polypharmacologic approach of Donepezil and Memantine has demonstrated promise in the treatment of Alzheimer's disease, its drawbacks and possible hazards underscore the necessity for alternative therapeutic approaches. Given that natural chemicals have been demonstrated to have neuroprotective, anti-inflammatory, and antioxidant qualities, future research should concentrate on investigating their medicinal potential. These substances may provide a safer, more efficient, and more environmentally friendly method of treating Alzheimer's disease because they are sourced from plants, fungi, and other natural sources. Researchers can create innovative, evidence-based treatments that enhance the quality of life for Alzheimer's patients and their caregivers by clarifying the molecular processes behind the bioactivity of these organic substances. Some natural products that are currently in clinical trials include- Bryostatin, Dronabinol, Bezisterim, Melatonin, Curcumin, Pinitol, Tramiprosate, Resveratrol and so on.

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