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Review Article

Memantine and its role in parkinsonism, seizure, depression, migraine headache, and Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a neurological disorder characterized by mental and behavioral changes that develop progressively with a decline in brain function. Dysfunctions in glutamatergic and cholinergic pathways, along with an increased concentration of beta-amyloid protein (Aβ), lead to synapses that are full of phosphorylated protein. These changes result in several pathological, biochemical, cellular, and molecular alterations that increase neural excitation directly or indirectly at the neural level, affecting the synapse, axons, signal transmission, and all parts of neurons. All these alterations, with continuous excitatory effects, eventually lead to neural loss and degradation due to stimulation of the immune response.

However, memantine is a non-competitive antagonist of N-methyl-D-aspartic acid (NMDA) glutamatergic receptors of moderate affinity and voltage-dependent that blocks the effects of pathologically elevated glutamate tonic levels, which can lead to neuronal dysfunction. Memantine has shown improvement in cognition, global clinical status, activities of daily living, and behavioral disturbances in moderate and severe AD.

In this review, we will discuss the effects of memantine use and side effects, as well as its application in treating other diseases or pathological conditions with the prospective use of memantine or an alternative. Memantine is generally well-tolerated, and the most common adverse reactions are vertigo, headache, and hallucinations, which are usually mild.

Keywords

N-Methyl aspartate, Alzheimer Disease, Cholinergic Agents, Glutamates, Memantine

Introduction

Worldwide, Alzheimer's disease is a significant health concern that is associated with symptoms and diseases of aging (Bellenguez et al. 2022). Despite the availability of medicines that improve human health and increase lifespan in many countries, a specific cause or treatment that can stop Alzheimer's disease has not been found, and it is expected that the incidence of dementia and Alzheimer's disease will rise significantly over the next twenty years (Bellenguez et al. 2022).

The increase in the prevalence of Alzheimer's disease is also associated with a rise in high socio-health costs at the national level, which is expected to become even more significant in the future (Trevisan et al. 2019). This is a common trend for all chronic diseases, including hypertension, hyperglycemia, dementia, hyperlipidemia, uveitis (Akeel Naji 2021), and many others. Socio-health costs attributable to Alzheimer's disease increase parallel with functional impairment, cognitive impairment, comorbidity, and neuropsychiatric symptoms (Martin and Velayudhan 2020).

However, early diagnosis and treatment of Alzheimer's disease could reduce the socioeconomic cost of the disease. The goal of treatment is to delay the appearance of disease symptoms, reduce functional deterioration, improve patients' quality of life, and relieve the burden on family members and caregivers (Sonkusare 2005).

The impact of antidementia drugs, such as memantine, on cost-effectiveness can be measured through various parameters, including economic factors such as hospital admissions, delay in institutionalization, emergency care costs, need for more continuous care, and use of psychotropic drugs. Other factors are more related to the quality of life of the patient and caregiver (Atri 2019).

This review highlights the role of memantine in Alzheimer's disease, ranging from its indications and contraindications to its ability to improve cognitive, behavioral, and functional symptoms, as well as the quality of life of patients.

Memantine and mechanism of its effect discovery and its role in Alzheimer

In 1966, memantine was discovered as a drug for treating hyperglycemia to treat high blood glucose. It has been shown not to have a significant effect on decreasing blood glucose. However, after this drug was developed in the enter clinical phases due to the prospect of an effect on the treatment of parkinsonism, seizure, depression, margin headache, and finally, Alzheimer's disease (Koola 2020).

As the only non-competitive NMDA receptor antagonist currently in clinical practice, memantine can inhibit the excessive activation of NMDA receptors to reduce excitotoxicity and protect neurons without affecting the physiological activation of NMDA receptors required for cognition (Companys-Alemany et al. 2020).

Clinical Guidelines for the Use of Memantine in Dementia

Many countries and institutions have decided to use memantine to treat Alzheimer's and reduce its symptoms. According to studies, some preferred memantine anti-acetylcholine esterase drugs, while others decided to leave it alone to treat Alzheimer's and reduce symptoms. For example, not loss, both the Behavioral Neurology and Dementia Study Group and the Neuropharmacology Group recommend memantine treatment in patients with probable or possible moderate or severe AD according to the NINCDS-ADRA criteria (National Institute of Neurologic, Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) (level of evidence I, grade of recommendation A). It is also commented that combined use with a cholinesterase inhibitor (ACEI) in these phases is more beneficial than monotherapy with acetylcholine esterase inhibitors (level of evidence II, grade of recommendation B) (Calhoun et al. 2018; Straathof et al. 2022).

NICE guidelines on the treatment of dementia

The National Institute of Health and Care Excellence (NICE) guidelines in the United Kingdom recommend memantine monotherapy in patients with moderate AD who are intolerant or have a contraindication to using acetylcholine inhibitors in patients with AD in the severe phase of the disease (Yunusa et al. 2021; Butterworth 2022).

For patients with an established diagnosis of AD who are taking acetylcholine inhibitors, the following is included:

a) Consider adding memantine with or without an acetylcholine inhibitor if you are in a moderate phase;
b) Consider adding memantine to the acetylcholine inhibitor if they are in an advanced stage.

Its prescription must be made under the following conditions: a) prescriptions made by specialists such as neurologists, geriatricians, and psychiatrists; b) other health professionals, such as primary care physicians, if they have an expert degree in the diagnosis and treatment of AD; and c) do not suspend treatment with acetylcholine inhibitors in people with AD solely based on advanced disease.

Cochrane: Memantine as a treatment for dementia

Memantine benefits patients with moderate to severe AD, and this benefit affects cognition, functionality, and psychological and behavioral symptoms. The association of memantine and acetylcholine inhibitors produces less deterioration than a placebo. However, memantine is probably not better in patients with mild AD than in a placebo.

Overall, the evidence for memantine for AD is of high quality, coming from many trials in thousands of pa-

tients. We can be confident in the AD results, but this is not the case in patients with other types of dementia (Calhoun et al. 2018).

Memantin's mechanism of action

Memantine is a non-competitive antagonist of NMDA (N-methyl-D-aspartate acid) glutamatergic receptors. These receptors are calcium channels, and through their action, high levels of glutamate are regulated, ultimately responsible for neuronal dysfunction and death (Abdulameer et al. 2022; Al-kuraishy et al. 2022).

Several studies are trying to understand the mechanism of action of memantine and its neuroprotective effects that decrease the level of excitatory neurotransmitters. So the use of memantine is not limited to Alzheimer's only. In the Straathof et al. study, memantine could help treat obsessive-convulsive disorder (OCD) and reduce abnormalities in dopaminergic neurons (Straathof et al. 2022).

Physiologically, memantine and magnesium occupy the same NMDA receptor and are mutually exclusive as long as the channel is not blocked in the presence of both compounds (Thangabalan et al. 2013; Salim Mahmood et al. 2022). Receptor blockade's amplitude and speed are dose-dependent. Growing data indicates that neurodegenerative dementia symptoms and disease development are influenced by dysfunctional glutamatergic neurotransmission, notably in NMDA receptors (Fig. 1).

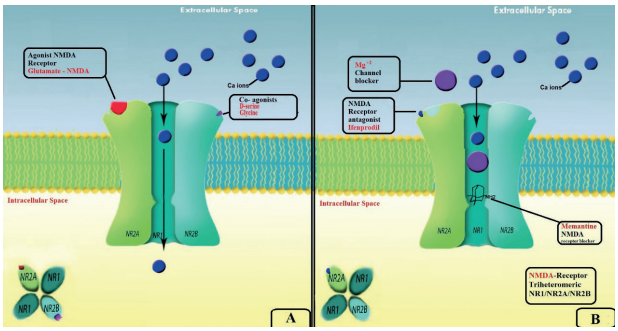

Figure 1. Illustrates the mechanism of action of memantine and the against an antagonist of NMDA receptors. (**A**) Show the site of binding of the agonist and co-agonist to the receptor site, which results in an increase in intracellular Ca and a neuroexcitatory, (**B**) Show the NMDA receptor antagonist or block the entry of Ca, which results in neuroprotection.

Indications for starting treatment

Memantine has been shown to improve cognition, global clinical status, activities of daily living, and behavioral changes in moderate and severe AD. Like acetylcholine inhibitors, although the overall benefit is modest, the interindividual response to memantine is variable (level of evidence I, grade of recommendation A) (Kamepalli Sujana et al. 2012; Al-Hussaniy et al. 2022d; Naji et al. 2022; Sai 2022).

Posology

The dose of memantine is well tolerated, reaching a maximum dose of about 28 mg daily. However, the dose can gradually increase every week to reach the maintenance dose to produce a better-tolerated effect with minimal side effects, and this can be achieved by gradually increasing the dose to 5 mg each week for the first three weeks as follows: memantine 5 mg at breakfast in the first week followed by 10 mg in the second, 15 mg for the third week, then the maintenance dose can be achieved in week four. The recommended maintenance dose is 20 mg per day. An equivalent liquid formulation can be adjusted easily and is suitable for patients that cannot tolerate tablet formulation (George and Kachappillil 2020; Rossignol et al. 2021).

The memantine tablet can be administered with or without food. However, the dose of memantine must be adjusted in patients with renal impermeant, especially when creatinine clearance reaches approximately (50 ml/minute / 1.73 m^2) in this case, the daily dose of memantine is approximately 10 mg per day (Table 1).

Table 1. Dosage of memantine.

Presentations	Posology
– Tablets 10 and 20 mg – Tablets 5, 10, 15, and 20 mg (initiator pack) – Or dispersible tablets 10 and 20 mg – Oral solution 5 mg/actuation	5 mg/day in the first week, increasing by 5 mg every week, up to 20 mg/day in 1 or 2 doses (10 mg in renal failure)

Treatment withdrawal

There are no evidence-based guidelines on when to withdraw this drug. It is recommended to evaluate its effect after six months of treatment. It is recommended to stop treatment if agitation, akathisia, or other neuropsychiatric symptoms appear and if the patient worsens globally faster than without treatment (Reeve et al. 2021).

Main contraindications or precautions

It is generally a well-tolerated drug, with adverse effects similar to placebo in some studies. The most frequent adverse effects are dizziness, constipation, drowsiness, headache, hypertension, and agitation. In patients with severe renal insufficiency, the dose should be reduced. It has no absolute contraindications, but caution must be exercised in epilepsy, renal failure, or urinary retention (Table 2).

Improvement of psychological and behavioral symptoms associated with dementia and cognitive symptoms

Psychological and behavioral symptoms associated with dementia are very common throughout the disease, appearing in up to 80% of patients during its evolution. A meta-analysis showed a significant improvement in agita-

Table 2. Adverse reactions of memantine.

Elevated liver function	Vertigo, balance, and epilepsy
Fungal infections	Heart failure
Drug hypersensitivity	Hypertension Venous thrombosis/thromboembolism
Drowsiness, confusion, hallucinations* psychotic reactions†	Dyspnea
Headache fatigue	Constipation vomiting pancreatitis

* Hallucinations: Patients with severe cases of Alzheimer's disease are the ones that experience hallucinations the most.

tion, illusions, disinhibition, and sleep-wake rhythm disorders compared to controls, slightly superior in managing hallucinations and irritability. In contrast, it presents similar results to controls in managing negative symptoms (dysphoria, anxiety/phobia, apathy, aberrant motor behavior, and eating behavior disorders) (Najim et al. 2021; Kim et al. 2022).

Regarding cognitive symptoms, a recent study revealed that the best drug to combat cognitive deterioration was memantine, followed by galantamine.

Functional improvement of patients and quality of life

The main objective of patients with dementia is to maintain functional autonomy. Evidence-based medicine recommends memantine, ACE inhibitors, physical exercise, and dyadic intervention to prolong functional autonomy and delay institutionalization. In patients treated with memantine monotherapy or biotherapy, *post hoc* analysis shows maintenance of daily activities compared to placebo, with consequent delay in institutionalization (Shaw et al. 2018).

On the other hand, memantine treatment has been shown to reduce caregiver stress and caregiver care time. In the few studies in this regard, combined therapy further enhances the concept of quality of life. The appropriate choice of treatment and therapeutic expectations is crucial, with real goals for the patient and the caregiver.

In the multicenter DOMINO-AD study ("Donepezil and Memantine in Moderate to Severe Alzheimer's Disease study"), variables related to the interruption of donepezil treatment or the start of memantine treatment were collected. Both patients who continued taking donepezil and those who started memantine showed less deterioration on the standardized Mini-Mental Test (SMMSE; $p < 0.001$) and on the Bristol Activities of Daily Living Scale (BADLS; $p < 0.001$) than those who discontinued donepezil or did not take memantine. Combination therapy (donepezil and memantine) was not significantly superior to donepezil monotherapy for primary or secondary endpoints. The post-analysis of the study data showed that abrupt discontinuation of donepezil increased the risk of worsening the condition within a few weeks of discontinuation and increased hospital admissions during the research period. Taken together, this is the most stressful moment associated with the poor quality of life that their caregivers envision. It is the most conflictive moment related to a worse quality of life perceived by their caregivers (Rajesh Kumar et al. 2014; Katsayal et al. 2021).

Impact in terms of healthcare care costs

Talking about dementia in economic terms is always undesirable. However, the reality is that it is one of the clinical entities that cause the most direct and indirect spending at the socio-health level. Combined therapy (ACEI and memantine) continues to be the most cost-effective approach from a health and social perspective, superior to treatment in monotherapy with ACE inhibitors. Studies show the real economic benefits of anti-AD therapies, both in favor of changing ACE inhibitors for memantine and continuing with ACE inhibitors (donepezil) (Katsayal et al. 2021; Sahu et al. 2021).

There are few studies concerning drug prescription in patients admitted to nursing homes. In indirect analyzes of health costs focused on drugs, it has been observed that the combination of therapies (ACE inhibitors and memantine) is the most cost-effective in reducing the costs derived from institutionalization in a residential center; therefore, its impact is not only economic but also in terms of health standards (Sahu et al. 2021).

Role of memantine in other neurodegenerative entities: frontotemporal dementia

Reviewing publications on the possibility of implementing symptomatic treatment in frontotemporal dementia (FTD) with memantine, a study published in 2018 brings together the results of clinical trials and case studies. The first, published in 2008, includes a family case of FTD, a behavioral variant, treated with memantine 10 mg twice daily. In this case, with a pathogenic mutation (R406W) in the MAPT gene (*microtubule-associated protein tau*), the author suggests that memantine could stabilize the progression of the symptoms of the disease.

However, the multicenter, randomized, double-blind, placebo-controlled clinical trial NCT00545974 evaluated the efficacy of memantine in mild to moderate FTD. It was concluded that memantine did not reduce symptoms in this type of dementia (Bang et al. 2015).

The latest Cochrane publication on the role of memantine in dementias addresses its potential use in FTD. It concludes that there is significantly little certainty in the evidence of its beneficial clinical effect on the GCR (global clinical rating) and behavioral symptoms compared to placebo. Similarly, there are no differences in cognitive function. However, for all results in efficacy, there is uncertainty, and the confidence interval is consistent with more than one conclusion. On the other hand, they con-

sider a great deal of discontinuity in the memantine group regarding therapeutic compliance (compared to placebo), which may be a source of confusion (Bang et al. 2015).

Basic and memantine research

Although memantine has been a consolidated drug in the symptomatic treatment of dementia for decades, basic research, essential in translational science, continues to focus on this molecule, revealing promising and interesting results in animal models and opening the possibility of a different clinical approval from the current one (Babiloni et al. 2013).

In a very recent article from 2021, this ability to impact the biological bases of AD is revealed, which, until now, is an enigma. In this work, a benefit is evidenced in the preclinical transgenic mouse model (homozygous Tg4–42) subjected to chronic treatment for four months with memantine at the level of cognitive performance (learning and memory tasks), behavioral symptomatology and pathological correlate, observing a reduction in loss of neurons in CA1 of the hippocampus, as well as decreasing neurogenesis impairment in the dentate gyrus. This effect, key in the mechanisms of neurodegeneration, reopens the debate on the potential usefulness of memantine in earlier phases of Alzheimer's disease, not only because of the clinical benefit described but also because of its action on the biology of the disease itself, making it a more than symptomatic treatment (Babiloni et al. 2013; Rosini et al. 2016; Al-Kuraishy et al. 2022).

Memantine and migraine headache

In the past, memantine was suggested to treat migraine headaches; However, the researchers show that some migraine sufferers have benefited from using memantine to treat migraine headaches (Shanmugam et al. 2019; Mahmood et al. 2023). Migraine headaches are characterized by moderate or severe head pain lasting anywhere from 4 hours to 7 days. The severity of migraine headaches can vary depending on patient factors such as age and genetics. Memantine has been found effective in treating chronic migraine sufferers who have failed other treatment options. This drug blocks certain receptors in the brain that can relieve pain caused by migraines and cluster headaches (Al_hussaniy et al. 2022a, c; Al_hussaniy 2023; Mahmood et al. 2023).

Memantine has also been found useful in treating depression; however, there are debates regarding its effectiveness for this purpose. Major depressive illness, bipolar disorder, postpartum depression, and seasonal affective disorder are just a few examples of the various forms of depression (Awad et al. 2022; Al_hussaniy et al. 2022b; Hussein et al. 2023). Depression is characterized by extreme sadness or a sense of worthlessness that interferes with normal daily activities. Memantine works by blocking neurotransmitters that cause brain cell damage and death when levels are too high. It also prevents excess glutamate from binding to NMDA receptors and causing inflammation and scarring in the brain. On the other hand, some believe that memantine is not very effective for depression because it only works for some patients and may cause side effects such as dizziness or headache in some patients (Hsu et al. 2022; Tawfeeq et al. 2022).

Conclusions

The indications for the use of memantine have been reviewed according to different clinical guidelines. The positive impact of the prescription of this drug in monotherapy and dual therapy in patients with Alzheimer's disease, according to the classic parameters of behavioral neurology, is highlighted. Possible indications in other entities, such as frontal lobe type dementia (DFT), have been discussed. It ends by opening the debate on its potential beneficial effect in earlier phases, both clinically and biologically, thanks to current basic science.

References

Abdulameer AA, Mohammed ZN, Tawfeeq KT (2022) Endoscopic characteristics and management of Subepithelial Lesions in Video-Gastascopie. Medical and Pharmaceutical Journal 1(1): 4–13. https://doi.org/10.55940/medphar20222

Akeel Naji H (2021) The Psychosocial and Economic Impact of Uveitis in Iraq. RABMS0 7(4): 207–215. https://doi.org/10.52547/rabms.7.4.207

Al_hussaniy HA (2023) Medical Scientific Research Challenges in Iraq. Medical and Pharmaceutical Journal 2(1): 1–3. https://doi.org/10.55940/medphar202228

Al_hussaniy HA, Al-tameemi ZS (2022a) Methicillin-Resistant Staphylococcus aureus and New Delhi Metallo beta-lactamases-types of antibiotic resistance, methods of prevention. Medical and Pharmaceutical Journal 1(1): 14–24. https://doi.org/10.55940/medphar20223

Al_hussaniy HA, AL-Biati HA, Ali IS (2022c) The Effect of Nefopam Hydrochloride on the Liver, Heart, and Brain of Rats: Acute Toxicity and Mechanisms of Nefopam Toxicity. Journal of Pharmaceutical Negative Results 13(3): e393. https://doi.org/10.47750/pnr.2022.13.03.061

Al_hussaniy HA, Altalebi RR, Albu-Rghaif AH, Abdul-Amir AG (2022b) The Use of PCR for Respiratory Virus Detection on the Diagnosis and Treatment Decision of Respiratory Tract Infections in Iraq. Journal of Pure and Applied Microbiology 16(1): 201–207. https://doi.org/10.22207/JPAM.16.1.10

Al_hussaniy HA, Mohammed ZN, Alburghaif AH, Naji MA (2022d) Panax ginseng as Antioxidant and Anti-inflammatory to reduce the Cardiotoxicity of Doxorubicin on rat module. Research Journal of Pharmacy and Technology 15(10): 4594–4600. https://doi.org/10.52711/0974-360X.2022.00771

Al-kuraishy AA, Jalil HJ, Mahdi AS, Al-hussaniy HA (2022) General anesthesia in patient with Brain Injury. Medical and Pharmaceutical Journal 1(1): 24–34. https://doi.org/10.55940/medphar20224

Al-Kuraishy HM, Al-Hussaniy HA, Al-Gareeb AI, Negm WA, El-Kadem AH, Batiha GE, Welson NN, Mostafa-Hedeab G, Qasem AH, Conte-Junior CA (2022) Combination of Panax ginseng CA Mey and Febuxostat Boasted Cardioprotective Effects Against Doxorubicin-Induced Acute Cardiotoxicity in Rats. Frontiers in Pharmacology 13: e905828. https://doi.org/10.3389/fphar.2022.905828

Atri A (2019) The Alzheimer's disease clinical spectrum: diagnosis and management. Medical Clinics 103(2): 263–293. https://doi.org/10.1016/j.mcna.2018.10.009

Awad M, Al-Hussaniy HA, Alburghaif AH, Tawfeeq KT (2022) The role of COVID-19 in myopathy: incidence, causes, treatment, and prevention. Journal of Medicine & Life 15(12). https://doi.org/10.1016/j.clinph.2012.09.017

Babiloni C, Del Percio C, Bordet R, Bourriez JL, Bentivoglio M, Payoux P, Derambure P, Dix S, Infarinato F, Lizio R, Triggiani AI (2013) Effects of acetylcholinesterase inhibitors and memantine on resting-state electroencephalographic rhythms in Alzheimer's disease patients. Clinical Neurophysiology 124(5): 837–850. https://doi.org/10.1016/S0140-6736(15)00461-4

Bang J, Spina S, Miller BL (2015) Frontotemporal dementia. The Lancet 386(10004): 1672–1682. https://doi.org/10.1038/s41588-022-01024-z

Bellenguez C, Küçükali F, Jansen IE, Kleineidam L, Moreno-Grau S, Amin N, Naj AC, Campos-Martin R, Grenier-Boley B, Andrade V, Holmans PA (2022) New insights into the genetic etiology of Alzheimer's disease and related dementias. Genetics of nature 54(4): 412–436. https://doi.org/10.1038/s41588-022-01024-z

Butterworth RF (2022) Memantine for the Treatment of Alzheimer's Disease: Novel Mechanisms and Future Opportunities. Neurology 4(3): 17–20.

Calhoun A, King C, Khoury R, Grossberg GT (2018) An evaluation of memantine ER+ donepezil for the treatment of Alzheimer's disease. Expert Opinion on Pharmacotherapy 19(15): 1711–1717. https://doi.org/10.1080/14656566.2018.1519022

Companys-Alemany J, Turcu AL, Bellver-Sanchis A, Loza MI, Brea JM, Canudas AM, Leiva R, Vázquez S, Pallàs M, Griñán-Ferré C (2020) A novel NMDA receptor antagonist protects against cognitive decline presented by senescent mice. Pharmaceutics 12(3): e284. https://doi.org/10.3390/pharmaceutics12030284

George D, Kachappillil AJ (2020) The level of Memory Impairment among elderly in a rural community of Ernakulam District. Asian J. Nursing Education and Research 10(1): 107–109. https://doi.org/10.5958/2349-2996.2020.00024.5

Hsu TW, Chu CS, Ching PY, Chen KW, Pan CC (2022) The efficacy and tolerability of memantine for depressive symptoms in major mental diseases: A systematic review and updated meta-analysis of double-blind randomized controlled trials. Journal of Affective Disorders 306: 182–189. https://doi.org/10.1016/j.jad.2022.03.047

Hussein ZR, Omar SK, Mustafa Alkazraji RA, Alsamarrai AN, Alrubaye HS, Al-Hussaniy HA (2023) Efficacy of Aflibercept as initial treatment for neovascular age-related macular degeneration in an Iraqi patient sample. Journal of Medicine & Life 16(2).

Kamepalli Sujana D, Sankar G, Abbulu K (2012) Simultaneous Estimation of Donepezil and Memantine by Reverse Phase HPLC in Bulk and Pharmaceutical Dosage Form. Research Journal of Pharmaceutical Dosage Forms and Technology 5(7): 958–961.

Katsayal BS, Lema AA, Jibrin K, Nuraddeen W, Alexander EM, Mohammed NH (2021) Ameliorative Role of Nutraceutical Quercetin and its Derivatives Against Cognitive Impairment Process Induced by Lead Exposure in Drosophila melanogaster (Fruit Fly). Iraqi Journal of Pharmaceutical Sciences 30(2): 135–142. https://doi.org/10.31351/vol30iss2pp135-142

Kim KN, Shah YB, Croy C, Lustig RA, LaRiviere M, Kotch C (2022) Life-threatening altered mental status secondary to memantine in an adolescent undergoing cranial radiotherapy for medulloblastoma. Journal of Oncology Pharmacy Practice: e10781552221102883. https://doi.org/10.1177/10781552221102883

Koola MM (2020) Galantamine-Memantine combination in the treatment of Alzheimer's disease and beyond. Psychiatry Research 293: e113409. https://doi.org/10.1016/j.psychres.2020.113409

Mahmood AS, Reyadh AR, Shareef BQ, Albu-Rghaif AH, Al-hussaniy HA, Naji MA (2023) Increasing Prevalence of Congenital Hypothyroidism in children with Down Syndrome who have a family history of Thyroid disease. Research Journal of Pharmacy and Technology 16(3): 1327–1334. https://doi.org/10.52711/0974-360X.2023.00218

Martin E, Velayudhan L (2020) Neuropsychiatric symptoms in mild cognitive impairment: a literature review. Dementia and Geriatric Cognitive Disorders 49(2): 146–155. https://doi.org/10.1159/000507078

Naji MA, Alburghaif AH, Saleh NK, Al-hussaniy HA (2022) Patient expectations regarding consultation with a family doctor: a cross-sectional study. Medical and Pharmaceutical Journal 1(1): 35–40. https://doi.org/10.55940/medphar20225

Najim SM, Moustafa MM, Hammodi LE (2021) Alzheimer's As a Metabolic Disease: A Review. Journal of Drug Delivery Technology 11(2): 617–624.

Rajesh Kumar D, Siva Shankar M, Prathap Reddy P, Ram Sarath Kumar B, Sumalatha N (2014) A Review on Alzheimer's Disease. Research Journal of Pharmacology and Pharmacodynamics 6(1): 59–63.

Reeve E, Farrell B, Thompson W, Herrmann N, Sketris I, Magin PJ, Chenoweth L, Gorman M, Quirke L, Bethune G, Hilmer SN (2019) Deprescribing cholinesterase inhibitors and memantine in dementia: guideline summary. Medical Journal of Australia 210(4): 174–179.

Rosini M, Simoni E, Caporaso R, Minarini A (2016) Multitarget strategies in Alzheimer's disease: benefits and challenges on the road to therapeutics. Future medicinal chemistry 8(6): 697–711. https://doi.org/10.4155/fmc-2016-0003

Rossignol J, Schinkel-Le Nagard N, Frenzel L, Hermine O, Greco C (2021) Substitution of opioids by N-methyl-D-aspartate receptor antagonists for treating pain in mastocytosis. Annals of Allergy, Asthma & Immunology 126(3): 293–295. https://doi.org/10.1016/j.anai.2020.11.013

Sahu D, Bhushan S, Das D, Kumar Debnath S, Barik L, Meena V, Singh V, Dixit AK, Prasad PVV (2021) Potential Ayurvedic Herbs for Neurodegenerative Diseases: A review. Research Journal of Pharmacology and Pharmacodynamics 13(2): 69–74. https://doi.org/10.52711/2321-5836.2021.00015

Sai KK (2022) Formulation Development and In vitro Evaluation of Memantine Hydrochloride Fast Dissolving Oral Films employing different grades of Hydroxy Propyl Methyl Cellulose. Research Journal of Pharmacy and Technology 15(1): 17–23. https://doi.org/10.52711/0974-360X.2022.00004

Salim Mahmood A, Ammoo AM, Ali MH, Hameed TM, Al-Hussaniy HA, Aljumaili AA, Al-Fallooji MH, Kadhim AH (2022) Antiepileptic Effect of Neuroaid on Strychnine-Induced Convulsions in Mice. Pharmaceuticals 15(12): e1468. https://doi.org/10.3390/ph15121468

Shanmugam S, Karunaikadal K, Varadarajan S, Krishnan M (2019) Memantine Ameliorates Migraine Headache. Annals of Indian Academy of Neurology 22(3): 286–290. https://doi.org/10.4103/aian.AIAN_294_18

Shaw C, Wagg A, De Santis R, Fitzgerald J, Adamis D, Molloy D, Timmons S, Meagher D, O'Regan N, Guilbault C, Baghdadli A (2018) CGS 38th Annual Scientific Meeting Advances in Care: From the Individual to the Technology. Canadian Geriatrics Journal: CGJ 21(3): 218–261. https://doi.org/10.5770/cgj.21.334

Sonkusare SK, Kaul CL, Ramarao P (2005) Dementia of Alzheimer's disease and other neurodegenerative disorders—memantine, a new hope. Pharmacological research 51(1): 1–7. https://doi.org/10.1016/j.phrs.2004.05.005

Straathof M, Blezer EL, Smeele CE, van Heijningen C, van der Toorn A, Buitelaar JK, Glennon JC, Otte WM, Dijkhuizen RM (2022). Memantine treatment does not ffect compulsive behavior or frontostriatal connectivity in an adolescent rat model for quinpirole-induced compulsive checking behavior. Psychopharmacology 14: 1–4.

Tawfeeq KT, Al-Khalidi GZ, Al-hussaniy HA (2022) Neurodevelopmental Abnormalities in Children Associated with Maternal Use of Psychoactive Medication: Maternal Use of Psychoactive Medication. Medical and Pharmaceutical Journal 1(2): 64–73. https://doi.org/10.55940/medphar202210

Thangabalan B, Sandhya C, Sunitha N, Manohar Babu S (2013) Stability Indicating RP-HPLC Method for the Estimation of Memantine Hydrochloride in Pure and Pharmaceutical Dosage Form. Research Journal of Pharmaceutical Dosage Forms and Technology 5(6): 334–340.

Trevisan K, Cristina-Pereira R, Silva-Amaral D, Aversi-Ferreira TA (2019) Theories of aging and the prevalence of Alzheimer's disease. BioMed Research International: e9171424. https://doi.org/10.1155/2019/9171424

Yunusa I, Alsahali S, Rane A, Eguale T (2021) Comparative value of cholinesterase inhibitors and memantine in persons with moderate-to-severe Alzheimer's disease in the United States: a cost-effectiveness analysis. Journal of Alzheimer's disease reports 5(1): 705–713. https://doi.org/10.3233/ADR-210307