CASE REPORT

Improvement of Depression and Cognitive Impairment with Memantine Therapy in Patient with Neuropsychiatric Systemic Lupus Erythematosus: Evidence Based Case Report

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ABSTRACT

Background: Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease that affects multiple organs. SLE can manifest neuropsychiatrically (NPSLE) with symptoms such as cognitive impairment, seizures, hallucinations, depression, and anxiety. Memantine is an NMDAR antagonist known to be effective as a treatment for cognitive disorders in dementia. **Objective:** To determine whether Memantine therapy can be administered for depression and cognitive impairment caused by autoimmune-related etiologies such as SLE. **Methods:** A systematic review of scientific evidence was conducted using an evidence-based approach. The search was performed on reliable databases, including PubMed, Cochrane, Scholar, Springer, and Medscape, using The Boolean Operator method. The keywords used were *Cognitive Impairment, Cognitive Disorder, Dementia, Depression, Organic Depression, Memantine, Systemic Lupus Erythematosus*, with filters set for publications from the last 15 years, human subjects, and English-language studies. **Results:** Three studies aligned with the clinical question. Study 1, conducted by Vidyanti et al., reported significant improvements in autoimmune dementia with the administration of Memantine at 10 mg. Study 2, by Czarnecka et al., reviewed Memantine's use in psychiatric conditions such as depression and schizophrenia and found supporting literature. Study 3, by Petri et al., reported improvements in several cognitive aspects in neuropsychiatric SLE. **Conclusion:** Evidence suggests that Memantine administration can improve cognitive impairment and depression in patients with NPSLE.

Keywords: Cognitive Impairment, Depression, Memantine, Systemic Lupus Erythematosus

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INTRODUCTION

Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) is a prevalent manifestation of SLE, with estimates suggesting a prevalence ranging from 37% to 95%[1]. Neuroinflammation plays a central role in the pathogenesis of neuropsychiatric systemic lupus erythematosus (NPSLE), a severe manifestation of systemic lupus erythematosus (SLE) that affects the central nervous system. The disease is characterized by immune-mediated injury involving autoantibodies, cytokines, and complement activation, which collectively disrupt the blood–brain barrier and promote neuronal damage. Elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have been implicated in driving microglial activation and synaptic dysfunction, contributing to cognitive impairment and psychiatric symptoms. Additionally, autoantibodies targeting neuronal and endothelial antigens exacerbate vascular inflammation, leading to ischemic injury and neurodegeneration. Neuroimaging studies in NPSLE patients often reveal cerebral atrophy, white matter lesions, and vascular occlusions, consistent with chronic inflammatory insults. Importantly, neuroinflammation in NPSLE is not only a driver of acute neurological events such as seizures and psychosis but also underlies long-term neurodegenerative processes, highlighting the need for early recognition and targeted immunomodulatory therapies. Recent reviews emphasize that the interplay between systemic autoimmunity and localized neuroinflammatory cascades is key to understanding the heterogeneity of NPSLE presentations, ranging from mild cognitive dysfunction to severe cerebrovascular disease[2,3,4].

NPSLE is broadly categorized into central and peripheral nervous system involvements. Central NPSLE is further subdivided into neurological and psychiatric manifestations. Central Neurological Manifestations: these include acute confusional state, aseptic meningitis, cerebrovascular disease, cognitive dysfunction, demyelinating syndrome, headache (including migraine and benign intracranial hypertension), movement disorders (chorea), myelopathy, and seizure disorders. Central Psychiatric Manifestations: these encompass anxiety disorders, mood disorders, and psychosis.

Cognitive impairment is among the most frequently observed NPSLE conditions, affecting approximately 38% of SLE patients. Neuroimaging modalities—including MRI, fMRI, and PET scans—have identified significant structural and functional alterations in these patients. Key findings include reduced brain volume in the hippocampus and amygdala, alongside diminished white matter integrity across various cerebral regions[5].

Mood disorders are also frequently identified in patients with SLE, with depression exhibiting a prevalence of approximately 25%. Anxiety is even more prevalent, affecting roughly 37% of this population, whereas psychosis remains a relatively rare manifestation. Psychotic symptoms typically emerge in correlation with increased disease activity or systemic exacerbations; however, they generally demonstrate a favorable prognosis following appropriate therapeutic intervention. In cases of psychiatric disorders secondary to NPSLE, the administration of antipsychotics, antidepressants, and anxiolytics has been shown to yield positive clinical outcomes and a high rate of recovery[6].

Memantine is a drug that functions as an antagonist of the N-Methyl-D-Aspartate (NMDA) glutamate receptor, inhibiting extra synaptic NMDA receptors to reduce the excitatory effects of glutamate. Excessive glutamate excitatory activity has been linked to white matter injury in oligodendrocytes within the myelin sheath, contributing to demyelination, which in turn affects cognitive decline[7].

Additionally, glutamate also plays a role in psychiatric disorders such as depression, where elevated levels of glutamate have been observed in subcortical brain regions, along with a significant loss of glial cells responsible for glutamate cycling in the frontal region of patients with depression[8].

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that can cause chronic neuroinflammation in the central nervous system through increased pro-inflammatory cytokines and demyelination, leading to depression, cognitive impairment, and an increased risk of dementia[9.10]. However, further evidence-based investigation is required to determine whether Memantine can be used to treat cognitive impairment and depression associated with autoimmune diseases such as SLE.

CASE

A 35-year-old woman was diagnosed with systemic lupus erythematosus (SLE) three years ago. She was hospitalized twice within the past three months due to neuropsychiatric symptoms of SLE, including acute confusion syndrome, memory impairment, disorientation, language association difficulties, concentration problems (slowed response time in conversation), derealization, visual hallucinations, and moderate depression. Blood laboratory results were within normal limits, while MRI with contrast revealed encephalomalacia and cerebral atrophy as a consequence of a previous stroke infarct that occurred 10 years ago due to antiphospholipid syndrome.

During both hospitalizations, the patient received methylprednisolone injections (125 mg, three times daily) and showed improvement in concentration and resolution of visual hallucinations. However, memory impairment persisted for several weeks, leading to the initiation of Memantine therapy (5 mg daily) after the second hospitalization.

Following Memantine 5 mg treatment, the patient's depressive symptoms improved. Subsequently, the Memantine dosage was increased to 10 mg once daily, resulting in enhanced cognitive function, including improvement in memory, response time, and language association. The patient's mood stabilized, and she was able to resume daily activities as usual.

METHODS

The literature search was conducted using search engines from reliable sources such as PubMed, Cochrane, Scholar, Springer, and Medscape, applying the Boolean Operator method with the following keywords: Cognitive Impairment, Depression, Memantine, Systemic Lupus Erythematosus. The search was filtered for journal publications from the past 15 years, human subjects, and English-language studies. Subsequently, several relevant articles were selected based on the topic under discussion.

Clinical Question Formulation

In this case, the following clinical question is identified: Can Memantine be used in patients with SLE experiencing neuropsychiatric symptoms (depression and cognitive impairment)?

P (Patient/Problem) : SLE patient
I (Intervention) : Memantine
C (Comparison) : -
O (Outcome) : Neuropsychiatric symptoms

Evidence Search Methodology

The search for scientific evidence was conducted through a systematic evidence-based approach, utilizing reliable journal databases such as PubMed, Cochrane, Medscape, Springer, and Scholar. The search was performed using The Boolean Operator method with the following keywords: *(Memantine) AND (cognitive impairment) AND (depression) AND (Systemic Lupus Erythematosus).*

Following title and abstract screening, as well as applying inclusion and exclusion

criteria, three journals were identified that were relevant to the clinical question.

1. Vidyanti AN, Maulida Awaliyah MTN, Fauzi AR, Harahap ISK, Mulya DP. Dementia in a patient with autoimmune disease and hypercoagulable state worsened by COVID-19 vaccination: A case report. Ann Med Surg (Lond). 2022 Jun;78:103886. doi: 10.1016/j.amsu.2022.103886. Epub 2022 Jun 3. PMID: 35677525; PMCID: PMC9163025.
2. Czarnecka K, Chuchmacz J, Wójtowicz P, Szymański P. Memantine in neurological disorders - schizophrenia and depression. J Mol Med (Berl). 2021 Mar;99(3):327-334. doi: 10.1007/s00109-020-01982-z. Epub 2021 Jan 14. PMID: 33447926; PMCID: PMC7900025.
3. Petri M, Naqibuddin M, Sampedro M, Omdal R, Carson KA. Memantine in systemic lupus erythematosus: a randomized, double-blind placebo-controlled trial. Semin Arthritis Rheum. 2011 Oct;41(2):194-202. doi: 10.1016/j.semarthrit.2011.02.005. Epub 2011 Apr 1. PMID: 21458845; PMCID: PMC3153605.

The next step involves conducting a critical appraisal of these journals. Details regarding the database search process and critical appraisal are provided in the attachment.

RESULTS

1st Study

Vidyanti AN, Maulida Awaliyah MTN, Fauzi AR, Harahap ISK, Mulya DP. Dementia in a patient with autoimmune disease and hypercoagulable state worsened by COVID-19 vaccination: A case report. Ann Med Surg (Lond). 2022 Jun;78:103886. doi: 10.1016/j.amsu.2022.103886. Epub 2022 Jun 3. PMID: 35677525; PMCID: PMC9163025.

This study is a case report detailing the experience of a 44-year-old male who presented with severe cognitive impairment. His symptoms included short-term memory loss, forgetfulness, difficulty concentrating, disorientation while driving home, and verbal communication difficulties, alongside worsening weakness in all four extremities after receiving the COVID-19 vaccine. A CT scan revealed cerebral infarction, leading to a diagnosis of autoimmune dementia. The patient was treated with Memantine 10 mg as part of his cognitive rehabilitation therapy and showed significant improvement in cognitive function.

2nd Study

Czarnecka K, Chuchmacz J, Wójtowicz P, Szymański P. Memantine in neurological disorders - schizophrenia and depression. J Mol Med (Berl). 2021 Mar;99(3):327-334. doi: 10.1007/s00109-020-01982-z. Epub 2021 Jan 14. PMID: 33447926; PMCID: PMC7900025.

This study is a review of descriptive studies focusing on the use of Memantine for neurological disorders other than dementia, specifically schizophrenia and depression. It found that Memantine can shorten the time it takes for antidepressants to show clinical effects and enhance therapeutic response. This might be due to Memantine's role in modulating glutamate, which is found in elevated levels in the brain and blood of depressed patients, leading to toxicity. Memantine can also increase the production of Brain-Derived Neurotrophic Factor (BDNF), which plays a role in the etiology of depression. It demonstrates good synergy with all types of antidepressants, regardless of the dose. For treatment-resistant cases, Memantine's dosage can be increased to 20-40 mg.

3rd Study

Petri M, Naqibuddin M, Sampedro M, Omdal R, Carson KA. Memantine in systemic lupus erythematosus: a randomized, double-blind placebo-controlled trial. Semin Arthritis Rheum. 2011 Oct;41(2):194-202. doi: 10.1016/j.semarthrit.2011.02.005. Epub 2011

Apr 1. PMID: 21458845; PMCID: PMC3153605.

This study was a Randomized Controlled Trial (RCT) that compared Memantine administration versus placebo in two groups: a case group and a control group. It was found that Memantine given to patients with Systemic Lupus Erythematosus (SLE) with neuropsychiatric involvement, specifically cognitive decline, could improve several cognitive domains, such as simple reaction time and oral association.

DISCUSSSION

The results from the first study align with other research indicating a higher risk of dementia in autoimmune conditions, including Systemic Lupus Erythematosus (SLE)[9,13]. The case discussed in the first study is also similar to a case reported a year later by Praveen et al.[14] in another country; however, that case report did not specify whether Memantine was used to manage cognitive impairment in autoimmune dementia. The second study is consistent with other reviews recommending NMDAR antagonists for depression[8]. The third study, while showing no significant overall difference between the Memantine and placebo groups, did reveal significant improvements in two cognitive domains: simple response time and language association.

Table 1. Comparation of the Study

Study	Vidyanti et al., 2022(11)	Czarnecka et al., 2021(12)	Petri et al., 2011 (13)
Design	Case report (LoE 4d)	Systematic review of descriptive study (LoE 4a)	Randomized Control Trial (LoE 1c)
Data	1 case report from Indonesia	38 literatures about Memantine use for depression	One single center data divide as 2 groups and observed for 12 weeks
Subject	44 years male with autoimmune dementia	-	51 SLE patients
Exposure	Memantine	Memantine	Memantine
Result	Significant improvement in the cognitive function	Memantine can be used as depression augmentation	Memantine shows improvement in two domains of cognitive: simple reaction time dan oral association

NMDA receptor antagonists, such as ketamine, are already known for their use in treating depression, particularly severe depression and treatment-resistant depression[15]. Memantine, another NMDA receptor antagonist, is commonly used to improve cognitive decline in patients with Alzheimer's dementia. As a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, memantine reduces excitotoxicity caused by excessive glutamate signaling, which is implicated in neurodegeneration and cognitive decline. In dementia, particularly Alzheimer's disease, memantine has been shown to improve cognition, daily functioning, and global clinical status by modulating glutamatergic transmission and protecting neurons from calcium overload. Beyond dementia, clinical trials and reviews suggest that memantine may have off-label benefits in mood disorders, including major depressive disorder, due to its ability to regulate glutamate pathways that are linked to synaptic plasticity and mood regulation[16]. Given the similar mechanisms of action between ketamine and Memantine[8], a 2018 study suggested that Memantine's ability to improve brain-derived neurotrophic factor (BDNF) and neurogenesis could contribute to clinical improvement in depression[15,17]

(15,17). Furthermore, Memantine may prevent myelin damage, which frequently occurs in autoimmune encephalitis[18].

Several factors warrant consideration when administering Memantine to individuals with autoimmune conditions. Memantine is excreted renally, meaning any condition that increases urine pH (alkaline), such as renal tubular acidosis, severe kidney impairment (renal failure), or prolonged vomiting, can reduce Memantine excretion, potentially leading to increased blood levels. Therefore, dose adjustments are necessary for autoimmune patients with severe kidney impairment, such as those with Systemic Lupus Erythematosus (SLE) involving the kidneys. However, if the patient derives significant benefit, Memantine remains a viable therapeutic option[19].

For patients experiencing cognitive decline and depression due to their autoimmune condition, Memantine is a compelling option. Its dual function as an anti-dementia agent with a mild antidepressant effect allows for its use either as monotherapy or as an augmentation to antidepressant medication if prescribed. Memantine administration is expected to aid cognitive improvement, which in turn can enable patients with depression and autoimmune conditions to engage in cognition-based psychotherapy, such as Cognitive Behavioral Therapy (CBT), a non-pharmacological treatment option for depression. It is important to note that Memantine does not replace the role of immunomodulators in autoimmune patients, neither does antidepressant medication; rather, its function is to augment treatment for depression and to improve cognitive decline[20].

LIMITATION

A weakness of this Evidence-Based Case Report (EBCR) is the scarcity of studies involving NMDA receptor antagonists like Memantine in subjects with autoimmune conditions. Consequently, two of the studies identified have a low level of evidence. The first study in this EBCR is a case report, which has a Level of Evidence 4d according to the Joanna Briggs Institute Level of Evidence[21]. The second study is at Level 4a (a systematic review of descriptive studies).

APPLICATION OF EVIDENCE

The patient shares similar characteristics with subjects from both studies mentioned above, allowing the findings of those studies to be applied to this patient. The continued use of Memantine in the patient is justifiable as it has demonstrated evidence-based benefits.

CONCLUSION

Evidence suggests that Memantine administration can improve cognitive impairment and depression in patients with NPSLE.

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CONFLICT OF INTEREST

This research was conducted independently without affiliation with any specific institution or organization. All analyses and conclusions presented in this article are solely the work of the authors, free from any external influence.

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