Revolutionizing Neurorehabilitation: A Scoping Review of The Promising Role of Amantadine in the Recovery of Patients with Non-traumatic Brain Injury

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ABSTRACT

Background

Patients with severe nontraumatic brain injuries often present with disorders of unconsciousness. Immediate neurologic care, neuroprotection, and early neurorehabilitation are core principles for better outcomes. Neurorehabilitation, through both pharmacological and non-pharmacological strategies, aims to enhance neuroplasticity for faster recovery. Amantadine, primarily known as an antiviral and used in Parkinson's treatment, has shown a potential role for accelerating neuronal recovery and neurorehabilitation.

Objective

Available literature on the use of amantadine for nontraumatic brain injury patients is limited. This scoping review aims to identify the potential benefits and limitations of amantadine in neurorehabilitation.

Methodology

In the literature review, the keywords "Amantadine" AND "Neurorehabilitation" were used to search PubMed, EBSCO, and the Cochrane Library for articles published between January 1, 2003, and August 2024. Inclusion criteria required that articles have clear research objectives, strict subject eligibility criteria, a detailed methodology, and the administration of amantadine for nontraumatic brain injuries. Out of 57 identified articles, only 7 were included in the study.

Results and Discussion

Its benefits include improving the level of consciousness, accelerating recovery, decreasing mortality, managing delayed post-hypoxic encephalopathy, and improving verbal fluency in nonfluent speech. Its adverse effects and the paucity of available literature recommending amantadine for neurorehabilitation are the possible limitations.

Conclusion

Amantadine accelerates the neurologic recovery of patients with disorders of unconsciousness secondary to nontraumatic brain injuries.

Recommendation

Future studies may conduct meta-analyses, systematic reviews, and randomized controlled trials of amantadine in patients with nontraumatic brain injury to further strengthen its promising role in neurorehabilitation.

Keywords: *Amantadine, Neurorehabilitation, Non-traumatic Brain Injury*

INTRODUCTION

Patients who suffered from severe brain injuries may experience a decreased level of consciousness, or be patients with disabilities. Non-traumatic brain injuries include ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, hypoxic-ischemic encephalopathy, and brain tumors. Providing immediate standard of care and early neuroprotection and neurorehabilitation are essential for better clinical outcomes. Nevertheless, there remains a lack of evidence and clear guidelines for the neurorehabilitation of these patients.

Globally, according to the most recent Global Burden of Disease (GBD), stroke is the second leading cause of death and the third leading cause of disability. According to the study done by Fan et al. (2023), it is expected that by 2030, the global number of deaths due to stroke will increase to 4.90 million in total since 1990.[1] In the Philippines, the incidence rate of stroke ranged from 3.95% to 5.61%, while the prevalence rate ranged from 0.486% to 6.0% (Collantes, Zuñigam & Uezono, 2022).[2] This is further complicated by the current social conditions in the Philippines, wherein there is a poor neurologist-to-patient ratio, and the lack of decentralization to rural areas to provide neurologic care (Navarro, Baroque, Lokin, & Venketasubramanian, 2014).[3] Based on this epidemiological data, there is a high neurologic burden that has implications clinically, medically, physically, mentally, and economically. Thus, there is a need to provide the necessary management not only in the acute phase but also in the long-term management of patients, particularly to reduce the disability burden.

Neurorehabilitation is a promising field of medicine in which both pharmacological and non-pharmacological interventions are used to provide neurologic care and recovery across the phases of brain injury, from acute to long-term care. The main principle behind neurorehabilitation is to minimize the progression of the inflammatory cascade that drives neuroinflammation and to promote neuroplasticity. Neurorehabilitation includes neural regeneration, repair, dynamic reorganization of functional neural systems, and neurophysiological stimulation (Barrett, Oh-Park, Chen, & Ifejika, 2013).[4] There is only limited data regarding the pharmacological intervention when it comes to neurorehabilitation. However, one of the most widely used neurostimulants in neurorehabilitation is amantadine.

Amantadine is a known drug initially used as an antiviral agent against Influenza A. In the field of neurology, amantadine is widely used as an adjunct treatment for Parkinson's disease. This is due to amantadine's dopaminergic activity, which facilitates presynaptic release and blocks postsynaptic reuptake of dopamine. However, well-published studies already show that amantadine accelerated the recovery phase of patients with severe traumatic brain injury (Giacino et al., 2012).[5] This neurorestorative property is attributed to its NMDA receptor antagonist effects. Blocking the NMDA receptor prevents activation of glutamate receptors, reducing calcium ion influx. It is postulated that an excess of intracellular calcium ions activates calcium-dependent enzymes that are involved in inflammatory cascades that cause neuroinflammation, neuronal damage, edema, and neuroapoptosis.

There is only a scarce amount of evidence available about the utilization of amantadine in nontraumatic brain injury patients. This scoping review aims to identify and provide evidence for the potential benefits of using amantadine in the neurorehabilitation of patients with nontraumatic brain injury. By providing evidence of amantadine's promising potential for rehabilitation, this scoping review may pave the way for future studies on the neuroprotective effects of amantadine.

METHODOLOGY

Identifying the Research Question

Amantadine is a neurostimulant widely used for neurorehabilitation in patients with decreased levels of consciousness secondary to traumatic brain injuries. There are well-published studies that show that amantadine provides better outcomes in terms of neurologic recovery in traumatic brain injury patients. Hence, it is prudent to ask the following:

1. Does amantadine have a potential role in the neurorehabilitation of non-traumatic brain injuries?
2. What are the benefits of amantadine in the management of non-traumatic brain injuries?
3. What are the possible limitations of utilizing amantadine?

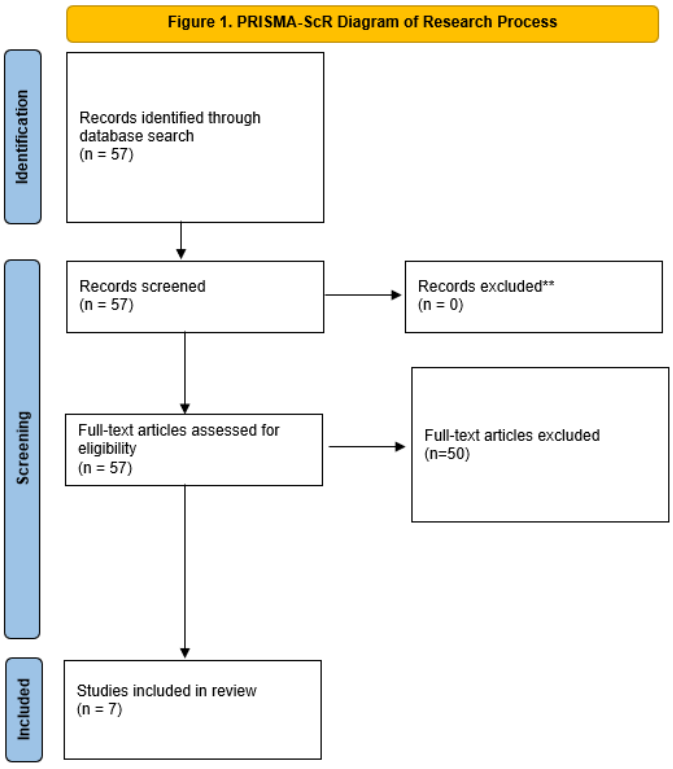
Identifying the Objective of the Scoping Review

This scoping review aims to determine the clinical benefits and limitations of utilizing Amantadine in nontraumatic brain injury cases. The specific objectives of the scoping review include:

1. Provide evidence of the benefits and possible indications of amantadine in nontraumatic brain injury patients.
2. Identify the probable limitations or hindrances in using amantadine clinically.
3. Give recommendation for future studies to further strengthen and provide more evidences regarding the utilization of amantadine in patients with non-traumatic brain injuries.

Protocol and Registration

A formal protocol was not registered for this scoping review. However, the review strictly adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) framework to ensure a reproducible and transparent methodology. The PRISMA-ScR Flow Diagram utilized for this scoping review is shown in Figure 1.



Information Sources and Search Strategy

The databases utilized in this scoping review include PubMed/MEDLINE, Cochrane CENTRAL, and EBSCO. All articles published between January 1, 2003, and August 2024 were selected. Core search terms were combined using Boolean logic to ensure reproducibility and broad coverage across databases. The full electronic search strategy utilized in PubMed (MEDLINE) was: ("Amantadine"[Mesh] OR "amantadine"[Title/Abstract]) AND ("Neurological Rehabilitation"[Mesh] OR "neurorehabilitation"[Title/Abstract] OR "Stroke"[Mesh] OR "stroke"[Title/Abstract] OR "Brain Injuries, Non-Traumatic"[Title/Abstract] OR "disorders of consciousness"[Title/Abstract] OR "hypoxic-ischemic encephalopathy"[Title/Abstract]). Similar adapted Boolean strings were utilized for EBSCO and the Cochrane Library.

Selecting Studies to be Included

The journal articles that would be included in this scoping review have to meet the following inclusion criteria:

1. Set of clearly formulated research objectives or questions
2. Well-detailed and strict eligibility criteria for the selection of subjects
3. Detailed and defined parameters and steps regarding the reproducible methodology
4. The study utilizes amantadine for the neurorehabilitation of patients with non-traumatic brain injuries, which include ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, encephalopathy, and brain tumors.

For this scoping review, the exclusion criteria include:

1. Journal articles written before 2003
2. Reviews or editorials
3. Utilization of amantadine in traumatic brain injuries, multiple sclerosis, and Parkinson's Disease.

Study Records

Data Management. The entire screening, selection, and data extraction processes were performed using a reference management software (Mendeley Reference Manager).

Screening and selection process. Initial screening consisted of a review of titles and abstracts. All studies deemed relevant to the scoping review were selected from the full-text articles. Any disagreements were resolved by consensus discussion.

Data extraction process. Extracted data included publication details (authors, year, and country where the study was conducted), study design, study population, utilization of amantadine, comparator, and main findings. Results were the outcomes measured in terms of the benefit and potential limitations of amantadine in the neurorehabilitation of patients with non-traumatic brain injury.

Data synthesis. The data were tabulated in a synthesis table. The data were then summarised qualitatively through narrative synthesis. Formal quantitative analysis was not within the scope of this review, as it could pave the way for further studies, such as systematic reviews and meta-analyses.

Risk of bias assessment. Risk of bias assessment is not necessary in scoping reviews. Accordingly, formal assessments of methodological quality were not performed.

Patient and public involvement. There was no involvement of any patients or any members of the public in this scoping review.

Charting of Data

The selection of articles used involved reading the titles and abstracts of the authors' results. These were assessed for relevance based on the authors' inclusion and exclusion criteria. The relevant full-text articles were then obtained and thoroughly read. Table 1 lists the full-text articles read and reviewed by the authors.

Researcher, Year of Publication	Country	Study Design	Study Population	Intervention	Comparator	Outcome
Arciniegas, D. B., Frey, K. L., Alan Anderson, C., Brousseau, K. M., & Harris, S. N., 2004	United States of America	Case Report	Patient with delayed post-hypoxic demyelination/ encephalopathy secondary to hypoxic-ischemic injury	Amantadine therapy in a patient with delayed post-hypoxic demyelination/ encephalopathy secondary to hypoxic-ischemic injury after 18 hours of depressed cardiopulmonary function following an overdose of methadone and diazepam	Period of no amantadine nor any neurostimulant given during the off period	There was a significant improvement in the cognitive and motivational impairments following the Amantadine regimen. There was a gradual return of the patient's independence in activities of daily living after 2 weeks of Amantadine. During the off period or reduced dose of Amantadine from 100 mg twice daily to once daily, there was noted deterioration of the cognitive and neurobehavioral processes.
Barrett, A. M., & Eslinger, P. J., 2007	United States of America	The study was a retrospective chart review. It utilized an open-label, on-off protocol with multiple assessments per on-off period.	The population consisted of four consecutive participants undergoing inpatient neurological rehabilitation.The participants had a mean age of 51.75 years and a mean of 10.75 years of education. All subjects met the clinical criteria for transcortical motor aphasia, presenting with nonfluent speech and frontal lobe dysfunction of the amotivational type. The etiologies for their condition included stroke for two patients, stroke post-aneurysm surgery for one patient, and brain tumor resection for one patient.	On-off protocol of Amantadine regimen in patients undergoing inpatient rehabilitation with transcortical motor aphasia and nonfluent speech due to stroke, stroke post-aneurysm surgery, or brain tumor resection	Speech therapy alone for nonfluent speech	Amantadine significantly improved word generation on the Controlled Oral Word Association (COWA) test for patients with nonfluent speech. No noted adverse effects in the study

Researcher, Year of Publication	Country	Study Design	Study Population	Intervention	Comparator	Outcome
Bender, A., Eifert, B., Rubi-Fessen, I., Jox, R. J., Maurer-Karattup, P., & Müller, F., 2023	Germany	This publication is an S3 clinical practice guideline. It was developed through a systematic literature search, an evidence-based evaluation of interventions, and expert consensus.	The guideline focuses on adult patients suffering from severe quantitative disorders of consciousness (DoC) due to acute brain injury. This encompasses patients in a coma, unresponsive wakefulness syndrome (UWS), or a minimally conscious state (MCS).	Enteral administration of Amantadine up to 400mg per day in patients with disorders of consciousness (Coma, Unresponsive wakefulness, Minimally Conscious State)	Standard Therapy for the underlying causes of the disorders of consciousness	Enteral administration of Amantadine up to 400mg per day in patients with disorders of consciousness (Coma, Unresponsive wakefulness, Minimally Conscious State) improved more quickly than in placebo groups. Patients with unresponsive wakefulness due to intracerebral hemorrhage who were given Amantadine had a faster regain of consciousness.
Leclerc, A. M., Riker, R. R., Brown, C. S., May, T., Nocella, K., Cote, J., ... & Gagnon, D. J., 2021	United States of America	The study was a retrospective cohort study. It evaluated the clinical effectiveness and safety of neurostimulants using data extracted from electronic medication administration records and provider notes.	The study evaluated consecutive adult patients (≥ 18 years of age) admitted to the intensive care unit (ICU). The final evaluable cohort included 87 patients in the safety analysis and 79 in the clinical effectiveness analysis. The patients suffered from acute non-traumatic strokes, specifically intracerebral hemorrhage (ICH, 47%), ischemic stroke (IS, 33%), or subarachnoid hemorrhage (SAH, 20%). The median age was 66 years, and the majority were male (64%).	Administration of amantadine monotherapy, modafinil monotherapy, or a combination of both for at least 3 days for a patient with Ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage	Acute stroke patients who were not given any neurostimulants	Amantadine monotherapy for at least 3 days, with a starting dose of 100mg twice daily, improved the level of consciousness of patients with ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage. The most commonly observed adverse effect was sleep disruption, attributed to the new sleep medication. Other adverse effects noted were agitation, delirium, and seizures.

Researcher, Year of Publication	Country	Study Design	Study Population	Intervention	Comparator	Outcome
Li, J., Zhang, P., Liu, Y., Wu, S., Yi, X., Zhang, S., ... & Liu, M., 2021	China	The study was a retrospective, hospital-based cohort study utilizing propensity score matching (PSM) to compare clinical outcomes.	The study evaluated adult patients (≥ 18 years) with acute large hemispheric infarction (LHI) who were admitted to the hospital within 24 hours of symptom onset. The final cohort comprised 158 LHI patients who received conservative standard therapy (ST), with 31 receiving amantadine in addition to ST and 127 receiving ST alone.	Early amantadine treatment, combined with standard therapy, of 100mg twice daily, initiated within 24 hours after stroke onset and continuing for at least 3 days in patients with large hemisphere infarctions	Standard therapy in patients with large hemisphere infarctions	Patients given an early amantadine regimen combined with standard therapy have a significantly lower in-hospital mortality rate and 3-month mortality compared to patients who received only standard therapy
Rühl, L., Kuramatsu, J. B., Sembill, J. A., Kallmünzer, B., Madzar, D., Gerner, S. T., ... & Sprügel, M. I., 2022	Germany	The study was an observational cohort analysis. It pooled individual patient data (IPD) from five single-center observational studies (a mix of prospective and retrospective registries).	The study evaluated 294 eligible patients admitted to a neurological intensive care unit (ICU) between January 2012 and December 2015. These patients had non-traumatic brain injuries (NTBI), which specifically included: ischemic stroke (IS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), community-acquired bacterial meningitis (CABM), and status epilepticus (SE). A key inclusion criterion was that patients required mechanical ventilation for >7 days.	Amantadine in Non-traumatic brain injury (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, community-acquired bacterial meningitis, status epilepticus) patients	Non-traumatic brain injury patients not receiving amantadine	Amantadine significantly improved the level of consciousness of the non-traumatic brain injury patients in terms of improved GCS score at Day 5. Secondary outcomes also showed no increased mortality in the Amantadine arm compared with the placebo. Epileptic seizures are a potential adverse effect of using Amantadine
Xi, X., Li, Q., Wood, L. J., Bose, E., Zeng, X., Wang, J., ... & Wang, Q. M., 2022	China and the United States of America	The study was a retrospective study.It used network analysis to evaluate the complex interrelationships among clinical variables, employing Gaussian graphical models to estimate networks and Network Comparison Tests (NCT) to distinguish among them.	The cohort included 348 adult stroke patients (>18 years of age) whose stroke lesions were confirmed by CT and/or MRI. These patients were admitted to an acute inpatient rehabilitation hospital between March 2014 and June 2015 and had a hospital length of stay (LOS) of greater than 1 week. The patients were divided into two main network structures based on their Functional Independence Measurement (FIM) motor subscores on admission: a high-FIM motor group and a low-FIM motor group.	Amantadine administration in stroke patients with High-FIM (Functional Independence Measure)	Amantadine administration in stroke patients with Low-FIM (Functional Independence Measure)	The administration of amantadine reduced patients' length of stay in the high-FIM network structure.

RESULTS & DISCUSSION

The Current Role of Amantadine in Neurorehabilitation

1. Improving the level of consciousness.

Leclerc et al. (2021) conducted a retrospective study involving nontraumatic brain injury patients (acute stroke of either ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage), with the primary aim to determine whether neurostimulant administration of either amantadine monotherapy, modafinil monotherapy, or a combination of both would improve wakefulness.[6] To determine whether the subjects of the study are responders to neurostimulant, two of the three criteria must be fulfilled within nine days of neurostimulant administration: an increase of ≥ three points in GCS prior neurostimulant initiation, improvement of level of consciousness based on caregiver notes, and there was noted clinical improvement in the notes of the physical and occupational therapists. The modafinil arm of the study did not improve wakefulness, whereas the amantadine group showed significant improvement. A combination of both neurostimulants did not provide a better outcome. The most common starting dose for amantadine in the study was 100mg twice daily for both amantadine and modafinil. The primary outcome of the observational study of Rühl et al. (2021) is to determine whether there would be improvement of wakefulness after five days of amantadine initiation in patients with non-traumatic brain injury, including ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, community-acquired bacterial meningitis, and status epilepticus.[7] Improvement of wakefulness is defined as an increase of at least three points in GCS within five days after treatment. Secondary outcomes include the amantadine effect in terms of mortality, ICU delirium, and epileptic seizures. Amantadine was associated with emergence from unconsciousness at the fifth day of treatment, and associated with improvement of consciousness at the fifth day of treatment. The authors noted that the observed improvement may be secondary to amantadine, which increases metabolism in the frontoparietal network. Figure 2 shows the mechanism by which amantadine may possibly activate the frontoparietal network. There was no significant association between amantadine treatment and ICU delirium.

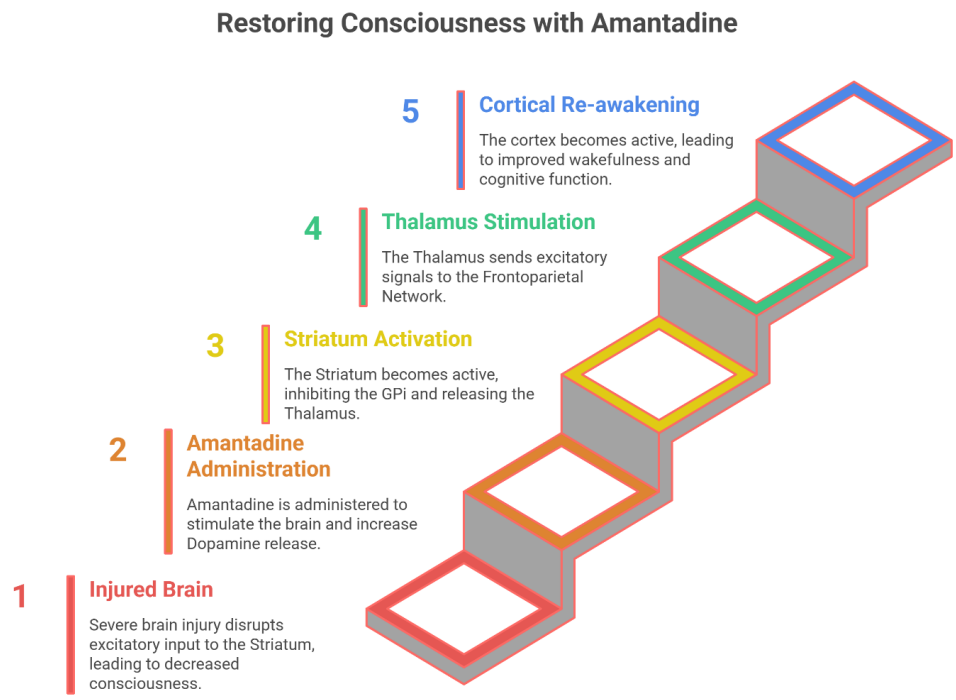
In the Clinical Practice Guideline on neurological rehabilitation in Germany (Bender, Eifert, Rubi-Fessen, Jox, Maurer-Karattup, & Müller, 2023), Amantadine was recommended as the primary pharmacological intervention to improve impaired consciousness in patients requiring neurological rehabilitation.[8] In patients with intracerebral hemorrhage and with an unconscious wakefulness state, treatment with amantadine provides faster recovery of the level of consciousness.

2. Accelerating Recovery and Decreasing Mortality

Li et al. (2021) conducted a retrospective study to determine whether amantadine, in addition to standard therapy, would accelerate or improve the recovery of patients with large hemisphere infarction.[9] In this study, 31 patients were given amantadine in addition to standard therapy, while 127 patients received standard therapy alone. The study concluded that amantadine, in addition to standard therapy, would accelerate recovery and significantly reduce in-hospital and 3-month mortality in patients with large hemisphere infarction.

Xi et al. (2022) conducted a network analysis by comparing stroke patients' responses to amantadine based on their Functional Independence Measure (FIM) levels. Based on this study, amantadine

Figure 2. The Mesocircuit Hypothesis: How Amantadine Restores Consciousness



administration reduced patients' length of stay in the high-FIM network structure.[10]

3. Enhancing Cognitive and Neurobehavioral Status in Delayed Post-Hypoxic Demyelination/ Encephalopathy

In a study done by Arciniegas, Frey, Anderson, Brousseau, & Harris (2004), amantadine treatment demonstrated improvement in terms of the cognition and neurobehavioral changes of a patient with delayed post-hypoxic demyelination/ encephalopathy secondary to hypoxic-ischemic injury after 18 hours of depressed cardiopulmonary function following an overdose of methadone and diazepam.[11] Delayed post-hypoxic demyelination is defined by delayed neurological deterioration, which starts from two days to six weeks after hypoxic-ischemic brain injury. The delayed neurologic deterioration includes progressive apathy, memory decline, executive dysfunction, and dependence in activities of daily living. There was improvement in memory, orientation, and executive function after three weeks of Amantadine administration. It was also observed that after tapering down Amantadine from 100 mg twice daily to once daily, there was a noted decline in attention, information processing, and executive function. Upon resuming Amantadine at 100mg twice daily, the improvements noted before the dose reduction were achieved. The authors of the study attributed these improvements to an additional mechanism of action of Amantadine: further augmentation of catecholaminergic afferents in neural circuits.

4. Role in Transcortical Motor Aphasia, Non-fluent Speech

It was postulated that dopaminergic agents can stimulate the circuits in patients with brain injury, causing frontal lobe syndromes. In the paper of Barrett, & Eslinger (2007), amantadine was utilized in an on-and-off protocol to check if there would be improvement of verbal fluency in

patients with nonfluent speech or transcortical motor aphasia.[12] Four patients were enrolled: two stroke patients, one stroke post-aneurysm surgery, and one brain tumor resection. The Controlled Oral Word Association (COWA) test was used to measure word generation. A significant improvement in word generation was noted after six days of amantadine treatment. Prior to amantadine treatment, participants had a mean of only 12.62 words on the COWA test, but it increased to 17.71 words after amantadine treatment.

Limitations of Amantadine in Neurorehabilitation

1. Adverse Effects

The usual reported adverse effects of amantadine are nausea, dizziness, and insomnia. This is also shown in the retrospective study by Leclerc et al., which found that the most common adverse effect was sleep disruption, leading to a new prescription for a sleep medication.[6] Other adverse effects noted by this study were agitation, delirium, and seizures.[6] In the observational study of Rühl et al., amantadine was associated with a non-significant 7.7% absolute increase in seizures.[7] Amongst the listed adverse effects, seizure is the most dreaded adverse effect of amantadine.[7] However, in the study conducted by Li et al., seizures were not observed in patients with large hemisphere infarction receiving amantadine.[9] They mentioned that the effect of amantadine on seizure threshold is dose-dependent. Higher doses of amantadine ($\geq$ 400 mg/day in adults) may induce seizures, while lower doses may elevate seizure threshold.

Ultimately, while the risk of adverse effects—especially sleep disruption and the dose-dependent risk of seizures—requires careful clinical monitoring, these risks must be weighed against the substantial life-saving benefits of amantadine. As noted earlier, adding amantadine to standard therapy notably decreases both in-hospital and 3-month mortality in severe conditions such as large hemisphere infarctions. Thus, strategic use of amantadine, particularly at lower doses, provides a highly favorable risk-benefit profile where the chances of survival and rapid neurologic recovery outweigh the manageable rate of adverse events.

2. Paucity of Guidelines Pertaining to Amantadine for Neurorehabilitation and Lack of Published Studies

After searching the available literature across databases, only the 2023 German Clinical Practice Guidelines in Neurological Rehabilitation by Bender et al. were identified, screened, and included in this scoping review.[8] Nevertheless, there is no mention of the dosage and duration of amantadine administration in non-traumatic brain injury patients. Furthermore, despite being recommended due to having the best available evidence, there is still no clear-cut indication when to initiate treatment with amantadine.

The paucity of clinical guidelines recommending amantadine for neurorehabilitation may be due to a lack of randomized controlled trials about the administration of amantadine to non-traumatic brain injury patients. It is also important to note that several variables must also be considered in conducting such studies, such as the demographics of the subject, the severity of the disorder of consciousness, the cause of the disorder of consciousness, standard therapy, and the case-to-case adjustment of the management depending on the clinical presentation of the patients. These factors may contribute to the difficulty in conducting randomized controlled trials using amantadine in non-traumatic brain injury. However, there are randomized controlled trials available using amantadine in cases of traumatic brain injury. This may pave the way for future studies concerning non-traumatic brain injury patients and the usage of neurostimulants.

3. Methodological Limitations of the Scoping Review Process

While this review underscores the clinical potential of amantadine, it is imperative to recognize certain methodological limitations inherent to the scoping process. Firstly, the literature search was restricted to three primary databases (PubMed/MEDLINE, Cochrane CENTRAL, and EBSCO) and confined to publications from January 2003 to August 2024. This restriction, coupled with the exclusion of grey literature, non-English publications, and ongoing unpublished trials, may have inadvertently excluded pertinent data. Furthermore, the application of stringent inclusion criteria resulted in a limited sample size of only seven heterogeneous studies, characterized by significant variations in study design, dosing protocols, and target populations. Lastly, as formal risk of bias assessments are not obligatory in scoping reviews, the overall methodological quality of the included evidence was not subjected to a formal evaluation. These limitations underscore the importance of conducting future comprehensive systematic reviews.

CONCLUSION

There is still a paucity of available literature about the administration of amantadine for faster recovery from disorders of consciousness. Despite this dilemma, amantadine has a promising role in the recovery of patients with non-traumatic brain injuries (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, status epilepticus, brain tumor, and community-acquired bacterial meningitis). Its benefits include improving consciousness and wakefulness, accelerating recovery, reducing mortality, enhancing cognitive and neurobehavioral status in delayed post-hypoxic demyelination/encephalopathy, and improving verbal fluency in non-fluent speech. Possible limitations of using amantadine are its adverse effects, such as sleep disruption and seizures, and the paucity of available literature and clinical practice guidelines recommending amantadine for neurorehabilitation.

RECOMMENDATION

This scoping review provides the various evidence and indications of using amantadine in nontraumatic brain injury patients. However, only a limited number of published articles are available to date. Future studies may include more articles for meta-analyses and systematic reviews as more studies are published. Lastly, randomized controlled trials of amantadine in nontraumatic brain injury patients may be done in order to further strengthen the available evidence regarding the promising role of amantadine.

ETHICS APPROVAL

Not applicable since this study does not involve human participants.

DECLARATION OF INTEREST

None.

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