# DISCUSSION

Safar's basic instruction says: "The patient surviving 5 minutes after head injury has to be considered a candidate for the final survival" [118]

Many secondary pathogenetic factors affecting human brain after injury can be positively influenced by pharmacotherapy.[119]

Extensive and very intense brain tissue irritation due to excitotoxic substances as glutamate, aspartate could be alleviated by means of neuroprotective molecules, as for example amantadine sulfate.[119]

Excitotoxic influence can provoke an intense intracellular calcium influx resulting in exaggerated neurocyte excitation which can initiate apoptosis and final neurodegeneration - active suicide.[119]

A component of Diffuse axonal injury (DAI) is believed to be present in all TBI caused by motor vehicle crashes in which the patient has lost consciousness and it is present in approximately one third of all severe TBI as indicated by pathological studies.[120]

DAI-associated TBI is characterized by widespread damage to axons in the cerebral hemispheres, the cerebellum, and the brainstem.[121]

The predominant anatomical sites of injury to the brain are most often the parasagittal white matter of the cerebral cortex, corpus callosum, and the pontine mesencephalic junction adjacent to the superior cerebellar peduncles.[120]

This area of the brain includes many dopaminergic pathways. Until now, clinical trials on therapeutic agents in TBI have been disappointing.[121]

This is most likely due to inclusion of TBI patients with different mechanisms of injury.[121]

Research suggests that the mechanism of injury may play a role in determining which factors mediate important components of the pathophysiology associated with TBI.[122]

There are likely unique neurochemical factors related to agonist receptor interactions associated with the mechanism of injury, whether it is cell wall disruption caused by contusive forces, ischemia, or DAI.[122]

In the present randomized by closed envelop method, placebo-controlled crossover study involving 60 patients with post-traumatic disorders of the consciousness, we found that the administration of amantadine between 1st and the 8th weeks after injury significantly improved the rate of functional recovery over the 4-weeks period of treatment, as compared with placebo, both groups had improvement during the 8-weeks period.

The primary outcome measures were the difference in slope between the groups over the course of treatment on four scales, the Disability Rating Scale (DRS), the Mini-mental

Status Test (MMST), The Glasgow Outcome Scale (GOS) and the Galveston Orientation and Amnesia Test(GOAT).

In group I there were trends toward a more rapid improvement during the first 4 weeks while on amantadine compared with group II, who were on placebo. However, what is remarkable is that after the patients were crossed over in the second 4 weeks, group II (now on amantadine) continued to improve, whereas group I (now on placebo) demonstrated little change.

At the end of the 8-weeks period there was no significant difference between the two groups as to the amount or level of recovery however the rate of recovery was more rapid in the amantadine group.

Patients who received amantadine had significantly better functional recovery on the DRS compared to those who received placebo over the four weeks of treatment.

The mean score on the DRS improved from approximately 19 to about 10 for those on amantadine and from 23 to about 16 for those on placebo. The relative gains, while modest, were nonetheless significant for this short time period that is also appear in MMST and GOS.

There were no significant effects on the rate of recovery with regard to the GOAT; the lack of effect with the GOAT scores was not unexpected, because memory is largely a cholinergic pathway.

The benefit of amantadine appeared to be consistent, regardless of the interval since injury or whether patients were in a vegetative state or a minimally conscious state at enrollment.

Although gains were generally well maintained in the amantadine group after the washout period, the rate of recovery attenuated substantially after treatment was discontinued.

This study could not absolutely demonstrate that earlier treatment was more efficacious than later treatment; it did demonstrate that the patients seemed to improve more rapidly while they were on amantadine.

Treatment with amantadine may have profound economic impacts in shortening the acute and rehabilitation length of stay after DAI-associated TBI, that appears on Comparing between the two groups according to days in intensive care as the mean of group I about 28 days and group II is about 36 days.

During the 8-week observation period, exposure to amantadine did not increase the risk of adverse medical effects.

Amantadine was well tolerated at a dosage of 200 mg/day throughout the study. There were no serious adverse side effects, and it seems to be quite safe. No patients required a change in dosage throughout the trial because of minor side effects.

There were no significant changes in laboratory values during the study or in any of the safety parameters.

These findings suggest that amantadine can be used safely at doses of 200 mg in patients with severe traumatic brain injury.

Our findings are consistent with a case report by *Zafonte et al*.[123] evaluated the impact of amantadine on cognition in a male who had been assaulted to the head with a blunt object.

The patient in that report presented with a GCS of 3, decerebrate posturing with minimal reaction to stimuli on the left, and an FIM score of 18 (totally dependent for care).

The patient showed improvement in his Coma Near Coma Score (CNC) as the amantadine dose was increased, and the score reached 0 on day 20 at a dose of 400 mg/day, as the dose was decreased, the CNC score worsened.

The dose of amantadine was increased to 400 mg/day and the CNC score again became 0. The patient was rehabilitated to become independent in his activities of daily living.

He was able to walk independently with a cane at discharge, and his FIM score was 83.[123]

Amantadine was withdrawn at 8 months without a decline in function with completion of outpatient rehabilitation.

These data demonstrated a dose dependent response relationship between amantadine and improvement in cognition and suggested that amantadine may be a reasonable option for treatment of a patient in a persistent minimally conscious state. [123]

*Wu and Garmel* [124] reported a female with improved ability to function after use of amantadine for TBI. She remained unresponsive after an MVA with a GCS of 6 and MRI showing minimal diffuse axonal injury.

After 6 doses of amantadine 150 mg, she could withdraw from pain, open her eyes spontaneously, and respond to her name. By day 7, she was alert and oriented, and with little assistance was able to carry out her activities of daily living. With continued physical and occupational therapy, she improved nearly to baseline. Objective measures of her neurologic improvement were not provided.[124]

In other study, retrospective evaluation included 12 patients who experienced head trauma done by *Nickels* [125] Outcome measures included functional, neurobehavioral, and cognitive status.

Nine subjects were classified as low-arousal. One of these subjects had mild under responsiveness and distractibility and experienced improvements in recall, retention, memory, orientation, concentration, and insight when amantadine 100 mg was administered twice daily.

Eight subjects who were classified as low-arousal with moderate-to-severe under responsiveness were given amantadine 150–200 mg twice daily.

Seven of these patients showed dramatic improvement in cognitive and physical function, while another patient showed improvement in response to stimuli.

Three other moderate to severe low-arousal subjects showed increased alertness, frequency of response, vocalization, mobility, and attention.

Discontinuation of the drug caused a decline in all improvements. Still, one other low-arousal patient showed improved processing time and awareness; one displayed improved response time and attention to task and orientation, and another showed improved alertness and improved motor skills.

Finally, one low-arousal subject showed no response. Overall, the study showed improvement in arousal.

Due to its retrospective nature, this study could not demonstrate a relationship between the time that amantadine was initiated post injury and possible benefit. Clinical evaluations were performed by non blinded staff.[125]

In a cohort study, *Hughes et al*.[126] evaluated patients with severe TBI who remained in a prolonged coma to determine the impact of amantadine on recovery of consciousness.

Amantadine was initiated an average of 6 weeks post injury. Improvements tended to occur within 1 week after initiation, with similar emergence from coma rates for amantadine and placebo. Selection and treatment biases rendered the groups not comparable.

Amantadine was given only to patients who remained at the trauma center. The control group was less likely to receive amantadine because they had a greater chance of being referred from a different center with the intention of returning to that center after becoming medically stable.

The study cases had a greater likelihood of being prescribed amantadine because they were more likely to be referred to the trauma center directly.

When selection bias was studied more closely, subjects who stayed in the trauma center receiving amantadine remained comatose longer compared with those who were transferred out and were not receiving amantadine (80.5 vs 50 days; $p = 0.0025$).

Due to its retrospective design, this study of Hughes et al[124] could not establish a relationship between the time that amantadine was initiated post injury and possible benefit derived from the drug. The study failed to demonstrate that amantadine had an effect on recovery of consciousness.[126]

A retrospective pilot study done by *Saniova*[127] on 74 patients aged 25–62 years who had sustained severe head injury compared changes in GCS scores and mortality results in patients receiving standard therapy either with or without amantadine.[127]

GCS scores in the amantadine group increased significantly but remained unchanged in the placebo group. The mortality rates were 6.06% ($n = 2$) for the amantadine group and 51.51% ($n = 17$) in the control group ($p < 0.001$) Physician-related selection is a potential limitation of this retrospective trial.[127]

In a randomized, double-blind, placebo-controlled, crossover study, *Schneider et al*[128] studied 10 TBI patients who were undergoing rehabilitation and had deficits in

attention and concentration to establish the efficacy of amantadine in improving cognitive and behavioral performance.

Outcome measurements included a number of standardized tests for orientation, attention, memory, behavior, and a composite variable of 18 different standardized neuropsychiatric tests.

Although patients showed substantial improvement over the 6-week study, there were no significant differences in rates of improvement for those receiving amantadine versus those receiving placebo.

Small sample size, lack of a homogenous population, short duration, and evaluation of acute benefits are limitations of this study. The length of time post injury was not stated.[128]

Another double-blind, randomized, placebo-controlled, crossover trial was done by *Meythaler* on 35 patients aged 16–75 years with TBI from MVAs to determine whether early use of amantadine was neuroprotective and whether later use would improve recovery.[129]

Amantadine was started 4–6 weeks post injury. Both amantadine and placebo therapy resulted in significant improvement in the MMSE, DRS, GOS.

Continued significant improvements in the above measures were noted in patients who received amantadine after crossover (6 wk).

The study showed more prompt improvement in function during the first 12 weeks after TBI, without regard to timing of initial therapy.[129]

Consistent improvements with amantadine therapy have been difficult to document for many reasons. First, some study designs were retrospective where biases in patient selection and treatment allocation could not be prevented.[130]

Highly variable spontaneous recovery occurs with TBI, making crossover designs problematic. This type of recovery could also obscure whether improvement was truly drug induced.[130]

Causes of TBI were often heterogeneous, and time from injury was also often variable and sometimes not stated, In addition, amantadine dosing and treatment duration were variable.[130]

A variety of outcome measures were used, making comparisons between studies difficult.

Clinical observations were likely performed by non blinded staff and may not have been performed by the same staff for all patients. Lastly, most of the studies were small.[130]

Nonetheless, available literature recognizes improvements in cognitive function (based on GCS) and other subjective parameters, as well as emergence from coma, during amantadine therapy in TBI.

Trials of pharmacotherapy for TBI are difficult to designand complete, making the development of evidence-based recommendations for therapy an ongoing challenge.[130]

To provide more definitive evidence regarding the potential role of amantadine in TBI, the Consciousness Consortium, an international research network, has undertaken a multicenter, randomized placebo-controlled trial of minimally conscious or vegetative patients.[130]

They are currently enrolling patients who are 4 –16 weeks post-TBI to determine the effects of amantadine therapy (up to 400 mg/day) on DRS scores.[131]

# SUMMARY

In the treatment of patients suffering from severe TBI, problems of arousal and attention(traditionally known as vigilance disturbances) and disturbances of drive are the central point of interest, since they can hinder therapeutic efforts in the areas of physiotherapy, occupational therapy, speech therapy and neuropsychology, especially where neurorehabilitationis concerned.(132)

A number of neurohormonal alterations have been noted after TBI. Reduced dopamine levels are noted consistently after TBI. Dopamine is thought to be involved in frontal lobe stimulation and plays a role in behavior, mood, language, motor control, hypothalamic function (including cognition),and arousal.(133)

A number of dopaminergic agents have been used to attempt to improve central nervous system function after TBI. The dopaminergic agonist amantadine enhances presynaptic dopamine release and inhibits dopamine reuptake, resulting in an increased amount of dopamine in the synaptic cleft. Amantadine may also increase the density of postsynaptic dopamine receptors and alter the conformation of these receptors.(134)

This study aimed to evaluate the effect of Amantadine in improving neurorecovery in TBI.

This study was carried out on 60 patients of both sex aged ranged from 16 to 75 years old fulfilled clinical criteria for adult patient with age more than 16 years, who directly admitted to the critical care Department with a TBI from MVC and a GCS score of <=10.

Patients were assigned into two equal groups by the closed envelope method.

- **Group I** thirty patients received amantadine in the first 4 weeks after injury and then placebo for the second 4 weeks.
- **Group II** thirty patients received placebo in the first 4 weeks and amantadine in the second 4 weeks.

Study excluded patients known to have severe ischemic heart disease or congestive heart failure, myocardial infarction, spinal cord injury with ongoing deficits or cancer, renal failure, penetrating head injury and pregnant females.

During the initial hospitalization full medical history was obtained including demographic data (name, age and sex), past medical history (CHF, IHD, Cancer, Renal impairment, Hepatic impairment, Stroke and epilepsy) Physical and neurological examination.

During the initial hospital admission, all patients were treated according to neurotrauma standard protocol, the neurotrauma protocols were outlined in the Guidelines for the Management of TBI.(113)

Patients had been followed up until discharge, not more than 56 days, the following were done laboratory examinations including: sodium, potassium, chloride, bicarbonate,

glucose, urea nitrogen, and creatinine and complete blood count obtained at 1st, 2nd, 3rd, 4th,5th,6th,7th and 8th week.

All patients start Amantadine, 200 mg/day, or a placebo was delivered in a double-blind randomized crossover study for 4 weeks (delivered in divided doses in the morning and at noon to improve alertness during the day) as soon as they were off pressors, and the neurosurgical consultant managing their acute care deemed them able to tolerate the delivery of amantadine.

No subject started the trial earlier than 4 days or later than 4 weeks after injury.

Patients had been followed up at 1st ,2nd, 3rd, 4th,5th,6th,7th and 8th week to assessment of neurological recovery using four different scales:-

1. The Disability Rating Scale (DRS): assesses function on eight activities, including eye-opening, communication, and motor response, with the highest score of 29 indicating the worst function.
2. The Mini-mental Status Test (MMST): is a brief 30 point questionnaire test that is used to screen for cognitive impairment, it take about 10 minutes and examines functions including arithmetic, memory and orientation.
3. The Glasgow Outcome Scale (GOS): is applies to patients with brain damage allowing the objective assessment of their recovery in five categories death, persistent vegetative state, severe disability, moderate disability and low disability.
4. The Galveston Orientation and Amnesia Test (GOAT) is a measure of attention and orientation especially to see if patient has recovered from post traumatic amnesia after TBI.

There was no statistically significant difference between 2 groups at admission as regards age, sex, past history of associated diseases.

There were no detrimental changes in laboratories during the study. Indeed, there was improvement in the blood urea, creatinine and hemoglobin from the admission point in the study.

However, this occurred regardless of the patients being on placebo or active drug and is most likely a reflection of the acute medical status of the patient rather than any effect amantadine had on these laboratory parameters.

The results of assessment of neurological recovery using four different scales show that in group I there were trends toward a more rapid improvement during the first 4 weeks while on amantadine compared with group II, who were on placebo.

However, what is remarkable is that after the patients were crossed over in the second 4 weeks, group II (now on amantadine) continued to improve, whereas group I (now on placebo) demonstrated little change.

Patients who received amantadine had significantly better functional recovery on the DRS compared to those who received placebo over the four weeks of treatment.

The mean score on the DRS improved from approximately 19 to about 10 for those on amantadine and from 23 to about 16 for those on placebo.

When comparing the amount of change between the two groups using DRS, MMST, GOS there was statistical difference in the recovery within the first 4 weeks between group I(on active drug) versus group II(placebo) $p < 0.001$ but no statistically significant amount of change during the second 4-week between group I (placebo) and group II (on active drug) that is appear due to variable spontaneous recovery occurs with TBI.

For GOAT there was no statistical difference in the recovery within the first 4 weeks between group I (on active drug) versus group II (placebo) $p = 0.220$ but statistically significant amount of change during the second 4-week between group I (placebo) and group II (on active drug) ($P = 0.011$),the lack of effect with the GOAT scores was not unexpected, because memory is largely a cholinergic pathway.

The benefit of amantadine appeared to be consistent, regardless of the interval since injury or whether patients were in a vegetative state or a minimally conscious state at enrollment.

Although gains were generally well maintained in the amantadine group after the washout period, the rate of recovery attenuated substantially after treatment was discontinued.

This study could not absolutely demonstrate that earlier treatment was more efficacious than later treatment; it did demonstrate that the patients seemed to improve more rapidly while they were on amantadine.

Treatment with amantadine may have profound economic impacts in shortening the acute and rehabilitation length of stay after DAI-associated TBI, that appears on Comparing between the two groups according to days in intensive care as the mean of group I is about 28 days and group II is about 36 days.

# CONCLUSION

1) Early improvement in some neurological and cognitive function after TBI may be obtained with early Amantadine therapy.

2) Amantadine can be used safely at doses of 200 mg in patients with TBI

3) Amantadine may have profound economic impacts in shortening the ICU length of stay after TBI.