CE 2.0 ANCC Contact Hours

Amantadine to Treat Cognitive Dysfunction in Moderate to Severe Traumatic Brain Injury

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of injury, disability, and death in the United States. Amantadine is an established dopamine agonist that supports neurological function. The purpose of this literature review was to determine whether amantadine improves cognitive function post-TBI. PubMed and CINAHL were used to search the literature for articles using amantadine to treat TBI from 1994 to 2004. Outcomes were summarized and the evidence was appraised. Although earlier studies from 1994 to 2003 were lower-level studies and recommended further research on treatment of cognitive dysfunction in TBI, the literature from 2004 to present generally concluded that amantadine improved cognitive function related to arousal, memory, and aggression. It can be started days to months postinjury and still produces benefits.

Key Words

Amantadine, Pharmacologic treatment, TBI, Traumatic brain injury

There are approximately 1.7 million traumatic brain injuries (TBIs) in the United States reported each year, accounting for 1.3 million emergency department visits, 275 000 hospitalizations and 52 000 deaths annually. According to the Center for Disease Control and Prevention, TBI encompasses one third of all injury-related deaths in the United States annually and is defined as any forceful impact to the head leading to brain dysfunction.[1] Traumatic brain injury ranges from mild injury or concussion to moderate and severe. Moderate to severe TBI is defined as loss of consciousness for greater than 30 minutes and having posttraumatic amnesia for 24 hours or longer.[1,2] Young children and adolescents are the 2 leading age groups to suffer from TBI, and older adults older than 65 years follow. Older adults older than 75 years are the leading age group to be hospitalized and/or die from TBI.[1] Falls, followed by motor vehicle crashes, are the 2 most common causes of TBI. Falls constituted 35.2% of all TBI, accounting for 50% of TBI incidence in age groups birth to 14 years old and 60.7% of adults older than 65 years. Although motor vehicle crashes are the second most common cause of TBI, they are the leading cause of TBI-related death (31.8%). Individuals with a history of TBI on disability accrue close to $50 billion annually. Patients with TBI are more at risk for cognitive dysfunction, psychiatric disorders, and aggression, making it essential to have proper pharmacotherapy available to treat symptoms.[3]

PATHOPHYSIOLOGY

Traumatic brain injury is a broad term that encompasses concussion, closed head injury, and blast-induced traumatic injury, which can cause different levels of neurological and chemical imbalances in the brain, leading to temporary or permanent disability. The external force that causes injury propels the brain to move rapidly inside the skull, resulting in damage to the gray matter and the cerebrovasculature.[4] The ensuing inflammatory process can last a few hours to days after the initial injury and causes neurological deficits with neurochemical imbalances developing hours after the brain injury because of nerve cell damage. This creates a disproportionate amount of glutamate receptors, free radicals, and intracellular calcium production, causing detrimental changes in ion homeostasis.[2]

The frontal lobe in the brain is the most common site of traumatic injury. It uses the neurotransmitter, dopamine, to regulate cognitive function and behavior, which is responsible for executive planning, attention, short-term memory, and motivation. When the brain moves rapidly in the head because of force, there is also the risk of diffuse axonal injury defined as the stretching and shearing of nerve axons in the brain and brainstem. Diffuse axonal injury is common in moderate to severe TBI and is characterized by some permanent cognitive dysfunction. Diffuse axonal injury and frontal lobe injury

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lead to changes in dopamine receptor function, as well as norepinephrine, acetylcholine, and serotonin receptor changes. Cognitive impairment is the leading cause of TBI-related disability in the United States, with as many as 43% of individuals who have suffered moderate to severe brain injury having some type of cognitive impairment.[4] Cognitive dysfunction is related to the severity of injury. Individuals with mild TBI may suffer mild cognitive dysfunction that fully resolves within 6 months of initial injury, whereas persons with moderate to severe TBI may suffer permanent and disabling damage. Common symptoms of cognitive and behavioral changes include aggression, irritability, decreased attention, impaired judgment, memory loss, and decreased mental flexibility. The severity of symptoms varies with the severity of brain injury.[4,5] Irritability and aggression occur in 29% to 73% of patients with TBI, and exact pathology is not fully understood. It has been hypothesized that aggression in individuals who have suffered a brain injury experience changes along the emotional pathways that alter sensory processing, cognitive appraisal, limbic drive, and cortical inhibitions.[6]

PHARMACOLOGY

Several different medications have been studied as treatment modalities for TBI. These medications include antipsychotics such as seroquel or haloperidol, benzodiazepines, anticonvulsants such as depakote, antidepressants, dopamine agents including amantadine, stimulants such as methylphenidate, and β-blockers such as propranolol.[3,7,8] Treatment modalities should be selected on the basis of the individual's medical history and symptomatology.[8] In patients with TBI with agitation and aggression, a Cochrane Review from 2006 found that the β-blocker propranolol was the most effective treatment regimen.[7] This finding is in agreement with another article that recommended guidelines for neurobehavioral problems experienced by patients with TBI.[3] In the same review, methylphenidate is recommended for treatment of attention deficit and decreased information processing in patients with TBI.[3]

Dopaminergic agents have been studied as a potential treatment for TBI on the basis of their favorable effect on dopamine in the central nervous system. Originally developed as an antiviral agent, amantadine has been used as an anti-Parkinsonian agent since the late 1960s.[9] Recently, its use has been studied in TBI.[10-12] Amantadine is hypothesized to increase release and reuptake of dopamine, causing increased concentration of dopamine in the synaptic cleft of neurotransmitters. Amantadine infusion in rats with TBI has been shown to increase striatal release and reuptake of dopamine while improving behavioral deficits.[13] Furthermore, amantadine may act as an *N*-methyl-D-aspartate antagonist resulting in neuroprotective effects.[10] In patients with TBI, amantadine may enhance cognitive function, concentration, processing time, psychomotor speed, and decreased fatigue. It has a favorable safety profile and is generally well tolerated by patients. Possible side effects include agitation, irritability, insomnia, vivid dreams, hyperactivity, delirium, depression, gastrointestinal upset, peripheral edema, and anorexia. Severe adverse effects may include seizures.[10,14] Side effects are often dose dependent and thus resolve with decreasing the medication dose or discontinuing it.[6,15] Although clinicians have evaluated amantadine's effects on TBI in the literature, results have been inconclusive. The purpose of this literature review was to evaluate whether amantadine is effective for increasing arousal and cognition after moderate to severe TBI and if so, when to start and how to dose the medication.

METHODS

A literature search using PubMed and CINAHL from January 1994 through February 2014 was conducted using the MeSH terms "amantadine," "pharmacotherapy," "traumatic brain injury," "TBI," "concussion," "post concussive syndrome," and "diffuse axonal injury." Articles written in the English language pertaining to pharmacologic treatment with amantadine within the first year of moderate to severe TBI were identified. Articles were peer-reviewed, evidence-based, full-text, and published in the United States, Europe, and Taiwan. Additional studies were obtained through searching the bibliographies of resultant articles. Resultant articles were a compilation of old (>10 years old) and new research examining amantadine treatment in TBI. Older research that was assessed included a Cochrane review,[7] a guideline for pharmacologic treatment of TBI,[3] 1 randomized controlled trial,[16] and a case study and case report.[5] Of the newer literature, 2 retrospective studies,[11,17] 1 retrospective case-control study,[14] 1 longitudinal observational cohort,[18] 1 meta-analysis,[2] and 4 randomized, controlled trials were examined.[6,10,12,13] Special consideration was given to the quality of evidence; newer studies generally were higher quality research, whereas older studies often consisted of individual case studies and/or randomized or nonrandomized, controlled trials with small sample size and potential selection bias. Standard outcome measures used most frequently in the literature included the Glasgow Outcome Scale (GOS),[19] Functional Independence Measure (FIM) and its FIM-cog subscale,[20,21] Disability Rating Scale (DRS),[22,23] and the Mini-Mental Status Examination (MMSE).[24] In addition, the authors corresponded through e-mail with an expert physician in the field to gain his insight regarding standard of care in TBI and use of amantadine for enhanced arousal and cognition. Finally, guidelines for TBI treatment were reviewed and considered. Findings were summarized in evidence tables by the authors, and quality of research was considered in developing a recommendation.

FINDINGS

Earlier Literature

Pharmacotherapy research studies using amantadine in TBI before 2004 (>10 years old) were considered earlier literature by the authors. Studies conducted before 2004 recommended further research or other pharmacologic therapies to treat cognitive dysfunction. Many of the studies had small sample sizes and were based on case reports or case studies. The Cochrane Database Review System, "pharmacological management for agitation and aggression in people with acquired brain injury" evaluated 6 randomized control trials published between 1986 and 1999, evaluating β-blockers, methylphenidate, and amantadine. The main results of the Cochrane Review concluded that β-blockers were better in treating aggression and agitation compared with amantadine; however, 3 studies were reviewed that analyzed β-blockers compared with 1 study using amantadine.[7] The study using amantadine was a double-blinded, placebo-controlled, crossover study that hypothesized that administration of amantadine would result in improved measures of attention, increased cognitive skills, and reduced agitated behavior in patients with TBI. It had a small sample size (n = 10). Participants were all from the same acute rehabilitation unit, and outcomes were measured using the Neurobehavioral Rating Scale and other neuropsychological tests in 5 domains: orientation, memory, attention, executive/flexibility, behavior, and composition variables in 2-week intervals. Results showed there was no benefit of amantadine treatment over placebo, and the hypothesis was not supported. There were many limitations of the study including limited sample size with only 2 participants actually finishing the entire trial, and the comparison of short-term effects of amantadine instead of potential of long-term benefits.[16]

A randomized, double-blinded, placebo-controlled, crossover study from 2002 (n = 35) examined patients with transportation-related TBI and Glasgow Coma Scale (GCS) scores of less than 10 in the first 24 hours after admission, loss of consciousness immediately after the accident, and traumatic amnesia lasting at least 1 week postinjury. Patients were divided into group 1 (n = 15) and group 2 (n = 20). Group 1 received amantadine 100 mg twice a day (bid) for the first 6 weeks and placebo the second 6 weeks, whereas group 2 received placebo first and amantadine second. Outcome measures included the MMSE, DRS, GOS, FIM-cog subscale for cognition and arousal, laboratory tests, electrocardiography, and urinalysis to test medication safety. There was significant improvement in group 1 compared with group 2 during the first 6 weeks for most outcome measures including the MMSE (P = .0185), DRS (P = .0022), GOS (P = .0077), and FIM-cog (P = .0033). There was also a significant improvement in group 2 during the second 6 weeks compared with the first 6 weeks via most outcome measures including the MMSE (P = .0409), DRS (P = .0099), GOS (P = .4008), and FIM-cog (P = .0173). Earlier treatment was not shown to be more efficacious, and there were no significant changes in laboratory tests, electrocardiography, and urinalysis between groups. It should be considered that the crossover design of this study may be problematic related to spontaneous improvement of patients with TBI with time in addition to the small sample size.[10]

Many previous studies had recognized that there was a lack of evidence-based guidelines pertaining to pharmacotherapy treatment of TBI.[3,10,16] In 2006, 3 panels of experts in the field of TBI worked together to form treatment guidelines for TBI in the domains of affect/anxiety/psychotic, cognitive, and aggression disorders. Articles used in the guidelines were scored using the Brain Trauma Foundation's Guidelines for the Management of Severe Head Injury that rates articles from class I through class III for evidence. The 3 studies cited regarding use of amantadine for the formation of the guidelines were categorized as class III evidence, the lowest ranking.[16] These studies included the first study reviewed previously from 1999, which was only finished by 2 of the 10 subjects[16] and 2 additional studies that were a case series (n = 6)[25] and a case report (n = 1)[26] examining the effects of a pharmacologic treatment combination of amantadine and L-dopa/carbidopa. After review of the literature, the guidelines determined that there was insufficient evidence to support one medication to improve cognitive function in TBI. Amantadine was recommended as a potential *option* for generalized cognitive functioning and to improve attention and concentration in moderate to severe TBI.[3] However, this is a weak recommendation considering it was based on lower-level research.

Recent Literature

Studies published over the previous 10 years, 2004 to present, were considered recent literature by the authors. Except for one retrospective cohort study,[17] the newer literature favors pharmacologic treatment of moderate to severe TBI with amantadine.[2,6,10-12,16] Results of the recent literature are summarized in Table 1. With the exception of one study, all research was conducted on humans. In the animal study, TBI was evoked with fluid percussion therapy in male rats (n = 130). Continuous amantadine infusion was shown to increase striatal dopamine release and reuptake while decreasing dopamine metabolism when compared with saline infusion and no treatment over a period of 8 weeks. Furthermore, rats treated with amantadine had improved behavioral function via novel object recognition and fixed-speed rotarod testing.[13] In adults with severe TBI 4 to 16 weeks postinjury (n = 184), amantadine improved DRS scores at a faster rate

TABLE 1 Summary of Recent Literature in Moderate to Severe TBI

Reference	Patient Population	Design	Pertinent Major Variables	Outcome Measures	Regimen	Results	Comments
Saniova et al[11]	n = 74; 25- to 62-y-old patients with severe head injury (GCS <8) admitted to ICU Group 1: n = 41 Group 2: n = 33	Retrospective pilot study	Amantadine and GCS, mortality rate	GCS on admission and discharge from ICU Mortality rate	Group 1: received amantadine 200 mg IV bid × 3 d started third day of hospitalization in addition to standard therapy Group 2: standard therapy only	GCS scores significantly increased from baseline in amantadine group ($P < .0001$) and were unchanged in placebo group Mortality rates decreased for amantadine group ($P < .001$)	Selection bias Retrospective design Short treatment interval Initial GCS of amantadine group higher than control group ($P > .05$)
Whyte et al[18]	n = 124; 4-16 wks post-TBI, patients 19- to 72-y old with DRS >15 on facility admission n = 58 patients treated with amantadine	Longitudinal observational cohort	DRS, psychoactive meds (including amantadine), medical complications, time until patient could first follow commands	DRS 16 wks postinjury, amount of time until patient could first follow commands	Patients monitored 16 wks post-TBI, differing amantadine dose	Amantadine treatment significantly associated with improved DRS when measured week to week; not significant when DRS rate improvement was calculated	Significance of amantadine changes based on statistical analysis Differing amantadine doses Selection bias
Hughes et al[17]	n = 123; subjects admitted to level 1 trauma center between 1990 and 1999, 17-87 y old, GCS ≤ 8, LOS >14 d, LC >1 wk after transfer from ICU (Rancho level <3) Amantadine: n = 28 Control: n = 95	Retrospective cohort study	Amantadine, emergence from coma, LC, GCS, SSEP, ISS	Rancho score, LC, GCS, SSEP, ISS	Differing doses of amantadine	Emergence from coma in 46% amantadine and 38% control patients ($P = .42$) Subjects prescribed amantadine had significantly longer LC ($P = 0.003$) Between those that did and did not respond to amantadine, no significant different between GCS, SSEP, and ISS	Selection bias Differences in case and control subjects Amantadine treatment in patients with LC, confounding variable Differing amantadine doses

(continues)

TABLE 1 Summary of Recent Literature in Moderate to Severe TBI (*Continued*)

Reference	Patient Population	Design	Pertinent Major Variables	Outcome Measures	Regimen	Results	Comments
Giacino et al[12]	n = 184; age 16-65 y, 4-16 wks post-non-penetrating head injury, vegetative or minimally conscious state (DRS score >11), inability to follow commands and functionally communicate	Randomized, placebo-controlled	Amantadine treatment and functional recovery (via DRS), rate of DRS improvement, adverse events	DRS during 4-wk treatment and during 2-wk washout period	Amantadine 100 mg bid × 14 d Increased to 150 mg bid at wk 4 Increased to 200 mg bid at wk 4 in DRS improved <2 points from baseline Tapered after 4 wks	Recovery via DRS improvement in amantadine group faster than placebo ($P = .007$) Slower DRS improvement of amantadine group during 2-wk washout compared with placebo ($P = .02$) No difference in adverse effects	One third of patients received confounding medications (ie, antiepileptic drugs, narcotics) Selection bias Brief treatment period
Hammond et al[6]	n = 76: participants >6 mos post-TBI CHI referred for irritability management, 16-65 y old, with prior enrollment score on NPI-irritability >2, all psychoactive medication dosing has been stable >1 mo and participants must have "observer" who lives with participant who can report signs of irritability n = 38 treatment n = 38 placebo	Parallel, randomized, double-blind, placebo-controlled	Amantadine treatment, NPI domain scores: irritability, aggression, and distress "Observer" participant's assessments of Beck's Depression Inventory-II, Brief Symptom Inventory, Global Mental Health Scale and Fatigue Impact Scale	Neuropsychiatric Inventory Irritability (NPI-I), Aggression (NPI-A), and Distress (NPI-D) pre- and posttreatment	Treatment group: 28 d of amantadine 100 mg bid in the morning and at noon Placebo group: 1 pill bid in the morning and at noon	Treatment group had 80.56% improvement of >3 points on the NPI-I. Compared with the placebo group had a 44.44% increase. Mean change in scores −4.3 with treatment compared with −2.6 in placebo group ($P = .0085$). Mean change in frequency and severity of irritability were statistically significant between treatment ($P = .0156$) and placebo groups ($P = .0055$). No mean change or statistical difference in NPI-Aggression and Distress scores between treatment and placebo groups. No statistical significant difference in changes in "Observer" BDI-II, Global Mental Health Scale or BSI-Anxiety scores	Improvement in moderate to severe irritability and aggression No apparent risk of administering amantadine 100-mg amantadine bid well tolerated in TBI patient's with CrCl >60 mg/dL Recommend larger sample size in the future. Safe and effective in treating TBI patients >6 mo postinjury with sufficient CrCl

(continues)

TABLE 1 Summary of Recent Literature in Moderate to Severe TBI (*Continued*)

Reference	Patient Population	Design	Pertinent Major Variables	Outcome Measures	Regimen	Results	Comments
Reddy et al[14]	n = 50; adolescents 13-19 y old with concussion with symptoms persisting 21-30 d postinjury n = 25 treatment n = 25 control Groups matched by age, sex	Retrospective case-control, pre-/posttest design	Amantadine treatment, verbal and visual memory, visual processing speed, reaction time, concussive symptoms	ImPACT and neuropsychological interview 21-30 d postconcussion Repeat ImPACT 40-50 d postinjury	Amantadine 100 mg bid × 3-4 wks	Significant decrease in symptoms ($P = .005$), verbal memory ($P = .009$) and increase in reaction time ($p = .05$) in amantadine group	Amantadine group had decreased verbal memory and visual memory and more symptoms compared with concussion group during pretest. Small sample size Nonrandomized Possible experimenter bias
Huang et al[13]	Male SD rats 6 wks old N = 130 total rats FSCV: n = 65 rats (n = 5 no injury, n = 15 low injury, n = 15 high injury, n = 15 high injury and saline tx, n = 15 high injury and amantadine tx). HPLC: n = 33 rats (n = 15 low injury, n = 15 high injury, n = 3 no injury). Behavioral tests: n = 32 rats (n = 9 no injury, n = 9 high injury, no treatment, n = 9 high injury, amantadine, and n = 5 high injury and saline)	Randomized, placebo-controlled, double-blinded	Fluid percussion-induced TBI, treatment with amantadine or saline, dopamine release and metabolism, cognitive and motor deficits	FSCV and HPLC to measure dopamine release and metabolism Novel object recognition (NOR) and FSRR behavioral tests used to measure cognitive and motor deficits	Rats subjected to different levels of injury (none, low, high) via fluid percussion to induce TBI Treatment with subcutaneous infusion of amantadine, saline, or no treatment for 8 wks Dopamine release at striatum and behavioral function measured at 1, 2, 4, 6, and 8, wks postinjury	Decreased striatal dopamine release, increased dopamine metabolism, and cognitive and motor impairment evident based on NOR and FSRR postinjury Amantadine therapy improved behavioral deficits, increased dopamine release and reuptake	

Abbreviations: bid, twice a day; CHI, closed head injury; DRS, Disability Rating Scale; FSCV, fast scan cyclic voltammetry; FSRR, fixed-speed rotarod; GCS, Glasgow Coma Scale; HPLC, high-pressure liquid chromatography; ICU, intensive care unit; ImPACT, Immediate Postconcussion Assessment and Cognitive Test; ISS, Injury Severity scale; LC, length of coma; LOS, length of stay; NOR, novel object recognition; NPI, Neuropsychiatric Inventory; SD, Sprague-Dawley; SSEP, somatosensory evoked potential; TBI, traumatic brain injury.

than placebo (P = .007) when given over a 4-week period. Doses were started at 100 mg bid for the first 2 weeks, increased to 150 mg bid during the third week, and increased again to 200 mg bid if the subject's DRS score had not improved greater than 2 points from baseline. During the washout period, DRS improvement rate in the treatment group slowed below that of the placebo group when amantadine was discontinued (P = .02), illustrating the beneficial effects the medication had on increasing rate of recovery in patients with TBI.[12] In another randomized, double-blinded, placebo-controlled trial that included patients with TBI 6 months postinjury with irritability (n = 76), amantadine 100 mg bid compared with standard treatment (eg, therapies and supportive measures) without amantadine was associated with a 80.56% improvement on the Neuropsychiatric Inventory-Irritability subscale compared with only a 44.44% improvement in the placebo group (P = .0016).[6] A retrospective case-control study of adolescents aged 13 to 19 years with postconcussive symptoms (mild TBI) 3 to 4 weeks postinjury (n = 50) found that amantadine 100 mg bid for 3- to 4-week duration had positive effects on symptoms (P = .005), verbal memory (P = .009), and reaction time (P = .05) via the Immediate Postconcussion Assessment and Cognitive Test compared with placebo group matched by age and sex.[14]

A retrospective pilot study from 2004 that included patients with severe TBI aged 25 to 62 years (n = 74) examined the impact of intravenous amantadine treatment 100 mg bid for 3 days (n = 41) versus standard treatment without amantadine (n = 33). Patients treated with amantadine had significantly improved GCS scores from baseline compared with unchanged GCS scores in the control group.[11] Although the results of this study favor amantadine, it is important to consider that the treatment window was extremely brief and that the GCS may not be the most reliable outcome measure on the basis of previous studies.[27,28] A meta-analysis of pharmacologic treatment for TBI supported the above study.[11] Eleven pharmacologic treatments for TBI in 22 different studies were evaluated and intravenous amantadine was recommended because of its improvement in the GCS after TBI.[2] In a longitudinal observational cohort of 19- to 72-year-old patients 4 to 16 weeks post-TBI (n = 124) with a DRS of more than 15 on facility admission, 58 were treated with amantadine. Dosing and duration differed on the basis of the observational nature of the study. Compared with those without amantadine treatment, the amantadine group was associated with improved DRS when measured from week to week. However, it is important to note that the results of this study were somewhat inconclusive. When the *rate* of DRS improvement was compared between groups, findings were not significant.[18] A retrospective cohort study from 2005 of subjects with severe TBI admitted to a level 1 trauma center from 1990 to 1999 with a length of coma greater than 1 week after transfer from the intensive care unit found no significant difference in emergence from coma between patients treated with or without amantadine. It is important to recognize that this study was not randomized, amantadine dosing differed, and those treated with amantadine had a longer length of coma, which is a potential confounding variable.[17] In the studies from the recent literature, amantadine treatment did not result in any significant difference in adverse effects compared with treatment without the drug.[6,12-14,17,18]

DISCUSSION

Research on pharmacologic treatment of TBI with amantadine has produced mixed conclusions and spans over 20 years. Evidence appraisal is imperative while reviewing the literature on amantadine use in TBI. Many of the earlier were not randomized, placebo-controlled, or blinded, and were based on small sample sizes, case series, or individual case studies. One must seriously question the conclusions from these studies on the basis of their design. The highest quality study from the earlier literature was favorable toward amantadine; however, it had a small sample size (n = 35) and differences were evident between the treatment and placebo groups.[10] The recent literature consists of higher-level studies and favors amantadine for increased arousal and/or cognition. Sample sizes were larger, and many of the studies were randomized and placebo-controlled. The treatment results from the recent literature are plausible considering the pathophysiology of TBI and the pharmacology of amantadine. As a dopaminergic agonist, amantadine has been hypothesized to increase the production and availability of dopamine whereas decreasing its metabolism and reuptake. This is advantageous for patients with TBI because it has been suggested that they are deficient in dopamine, a neurotransmitter that is essential for frontal lobe function.[4,10] The study in male rats[13] agrees with this hypothesis. It is important to consider the symptoms being treated in a patient with TBI. The recent literature mostly reviews amantadine's efficacy in increasing arousal and cognitions in patients with lethargy, coma, and low GCS scores. In patients with TBI with agitation or attention deficit as primary symptoms, amantadine may not be the best treatment modality as it may exacerbate these problems. β-Blockers, Seroquel, methylphenidate, or other medications may be more effective.[3,7] The side effects of amantadine are often dose dependent and resolve with decreased dosing of medication or discontinuation.[15] In the recent literature, each study was without significant adverse effects in the amantadine treatment gr oups.[6,12-14,17,18] Guidelines pertaining to TBI treatment were also reviewed. The Brain Trauma Foundation guidelines for in-hospital severe TBI do not address treatment with

amantadine or any of the other behavioral pharmacologic treatments discussed.[29] Behavioral symptoms are likely not addressed because these guidelines pertain to patients with severe TBI defined by a GCS of 3 to 8. Brain Trauma Foundation does not address treatment of moderate TBI in their guidelines. The National Guideline Clearinghouse was searched for TBI treatment guidelines. Cognitive enhancing treatment with multiple medications including amantadine, methylphenidate, and other stimulants, cholinesterase inhibitors, and dopamine enhancers are discussed in the Colorado Division of Workers' Compensation guidelines for TBI medical treatment. The document recognizes that Veteran's Affairs, the Department of Defense, and other studies support the use of amantadine in some patients with impaired cognitive function. It is important to monitor people on an individualized basis for side effects and treatment response. Trial decreases in dosing are recommended periodically for medication weaning.[8]

Considering that the higher-level evidence from our review showed that amantadine provided benefits compared with standard treatment and that safety of patients was not compromised with adverse effects,[10,14,18] we believe that amantadine may be considered a safe adjunct to standard treatment in patients with moderate to severe TBI.

Amantadine Dosing

In the recent literature, dosage varies between studies and is summarized in Table 2. In 2 studies, amantadine dose varied and was unknown because of their observational nature.[17,18] Of these studies, one found mixed results regarding amantadine's efficacy on the basis of statistical analysis[17] whereas the other did not find a significant association between amantadine and emergence from coma.[18] In another study, amantadine 200 mg bid was given intravenously[11] and was associated with increased GCS scores from baseline. The most common dose of amantadine in the literature where it exhibited efficacy in enhancing arousal post-TBI was 200 mg per day. Amantadine was started at 100 mg bid via oral or enteral route in 3 studies.[6,12,14] In one of these studies, amantadine was started at 100 mg bid; however, dosing was safely increased to 150 mg bid in week 3 and 200 mg bid in week 4 depending on how much the subject's DRS score improved from baseline.[12] In an older randomized, double-blinded, placebo-controlled crossover study from 2002, amantadine was also dosed at 100 mg bid.[10] On the basis of the literature, amantadine was effective at improving arousal and/or cognition when started at 100 mg bid. This seems to be a good initial dose of amantadine for most patients considering that they have adequate renal and liver function. Considering that amantadine's side effect profile is dose dependent, dosing should be individualized to the patient. Amantadine should be decreased or discontinued in patients exhibiting side effects including agitation, aggression, delirium, seizures, and apraxia. Behavioral toxicity has been noted with high amantadine dosing (400 mg/d)[15]; therefore, moderate dosing is favored.[10]

TABLE 2 Summary of Amantadine Dosing

Study	Amantadine Dose
Saniova et al[11]	200 mg bid IV
Whyte et al[18]	Differing doses, unknown
Hughes et al[17]	Differing doses, unknown
Giacino et al[12]	Amantadine 100 mg bid × 14 d
	Increased to 150 mg bid at wk 3
	Increased to 200 mg bid at wk 4 if DRS improved <2 points from baseline
Hammond et al[6]	100 mg bid in morning and at noon
Reddy et al[14]	100 mg bid
Meythaler et al[10]	100 mg bid

Abbreviations: bid, twice a day; DRS, Disability Rating Scale.

When to Start Amantadine

In the studies that demonstrated amantadine's efficacy in enhancing arousal in patients with TBI, the start time of the medication varied any time between 3 days and 6 months postinjury. The start time of amantadine for each study in the recent literature is summarized in Table 3. The earliest start time of amantadine was 3 days postinjury while patients were still in the intensive care unit.[11] In this study, amantadine was associated with increased GCS scores from baseline. In 2 studies, amantadine was

TABLE 3 Summary of Amantadine Start Time

Study	Start Time of Amantadine Treatment Related to Initial Injury
Saniova et al[11]	Day 3 of hospitalization post-TBI
Whyte et al[18]	Subjects in study were 4-16 wks postinjury; however, exact start time of amantadine unknown
Hughes et al[17]	Subjects had LOS in hospital >14 d with LC ≥ at least 1 wk after transfer out of ICU; however, exact start time of amantadine unknown
Giacino et al[12]	4-16 wks postinjury
Hammond et al[6]	>6 mos postinjury
Reddy et al[14]	21-30 d postinjury
Meythaler et al[10]	Anytime within 1-12 wks post injury; start time either within first 6 wks of injury *or* after 6 wks of injury

Abbreviations: ICU, intensive care unit; LC, length of coma; LOS, length of stay.

started between 4 and 16 weeks postinjury; one study found it was associated with the improved DRS score.[12] The other study found that DRS improved when analyzed week to week; however, overall rate of DRS improvement was not significantly associated with amantadine therapy.[18] When amantadine was started 3 to 4 weeks postconcussion in patients who persisted to have symptoms, it was significantly associated with decreased reaction time and increased verbal memory.[14] Even when amantadine was started as late as 6 months postinjury, it was significantly associated with positive outcomes such as decreased irritability.[6] Comparing these results to older studies, in 2002 amantadine treatment between 1 and 12 weeks postinjury was also associated with positive outcomes such as better scores on the MMSE, DRS, GOS, and FIM-cog subscale.[10] Considering the recent literature and one study from the earlier literature, amantadine was effective at improving arousal and/or cognition when started within a wide range of time postinjury. On the basis of these findings, we cannot recommend a specific time to start amantadine. Instead, it seems effective at increasing arousal and cognition and/or decreasing irritability in patients with moderate to severe TBI from 3 days to greater than 6 months postinjury.

Expert Opinion

Because research on the efficacy of pharmacologic treatment of TBI with amantadine is limited, the authors were interested in the opinion of an expert in the field regarding this therapy. A physician who serves as director of brain injury services at a nationally recognized rehabilitation facility in New Jersey was contacted via e-mail for an interview regarding current standard of care for TBI treatment. The expert was chosen on the basis of his multiple years of experience in the area of TBI evidenced by presentations for prestigious groups including the Association of Academic Physiatrists and the American College of Sports Medicine and speaking engagements on TBI at national conferences. The authors were interested in which patients the physician deemed appropriate for amantadine therapy. They also inquired about when to start amantadine and how to dose it. According to the expert, current standard of care is that amantadine can be started as early as 72 hours after admission if the patient is clinically stable and has adequate renal function. In his facility, it is used across the spectrum of injury severity. Initial amantadine dosing is 50 to 100 mg daily. Dosing may be increased by 50 mg every 2 to 3 days depending on tolerance and efficacy. Although severely injured patients may need more than 200 mg per day, higher-functioning patients may need less. Dosing is individualized to the patient. Maximum dose is 400 mg (Neil Jasey, e-mail communication, March 31, 2014).

The results of the literature review and recommendations are congruent with current standard of care. On the basis of the findings in the literature, amantadine is a safe adjunct to standard therapy for TBI. In the literature, amantadine was predominantly used in patients with moderate to severe TBI; however, it can be used effectively across the spectrum of injury. This recommendation is congruent with the study that demonstrated efficacy and safety of adolescents taking amantadine for postconcussive syndrome,[14] which is certainly on the lower spectrum of injury compared with moderate to severe TBI. On the basis of the standard of care and the literature, 200 mg per day of amantadine is appropriate; however, it may be prudent to start amantadine at a lower dose and increase gradually to 200 mg to minimize side effects. The literature demonstrated increased arousal and/or cognition associated with amantadine when started over a wide range of time postinjury (3 days to ≥6 months). This is congruent with expert opinion of using the drug as early as 72 hours postinjury.

CONCLUSION

Research in the last 10 years and expert opinion support amantadine as an effective medication with a low-side effect profile in helping patients with TBI with arousal, memory, and aggression. Clinicians can safely start amantadine in most patients at 100 mg bid and titrate the dose for desired outcomes in cognition and arousal. Amantadine may be initiated as early as 3 days to as late as greater than 6 months after injury depending on the patient's symptoms. Only one expert in the field of TBI was interviewed regarding standard of care treatment with amantadine. His bias toward amantadine use is a limiting factor in our recommendation. As amantadine is being seriously considered as an addition to standard TBI treatment, we recommend that further, high-quality research is conducted to reproduce the positive outcomes associated with amantadine treatment in TBI. A major limitation to future research on amantadine is funding; as a generic medication that has been used for years, researchers may have difficulty procuring funding to conduct large, high-level studies. This provides some explanation for the lower-quality studies in our review. Approximately 3% of severe TBI cases end in death annually, whereas there are 5 million Americans alive with disability secondary to TBI. It is imperative to find beneficial pharmacologic treatments, such as amantadine, to use as an adjunct to standard therapy to maximize cognitive function.[3,25] The minimal side effect profile of amantadine and its safe use demonstrated in the literature characterize this medication as a potential treatment to augment outcomes in patients with moderate to severe TBI.

KEY POINTS

- There is a collection of older (published before 2004) and newer (published 2004 to present) literature that examines the efficacy of amantadine for patients with TBI. Older literature is generally of poor quality (small sample size,

nonrandomized), whereas more recent publications have produced higher-level evidence (randomized-controlled trials, double-blinded, placebo-controlled, larger sample sizes).

- An assessment of the quality of research and the findings of higher-level studies lead the authors to conclude that amantadine pharmacologic therapy can produce favorable outcomes for patients with TBI. Amantadine treatment may lead to increased arousal and cognition post-TBI compared with placebo.
- On the basis of higher-level research that favored amantadine use, amantadine can generally be started at 100 mg bid anytime from 3 days to 6 months post-TBI for most patients. As is with all treatment recommendations, dose and time of therapy should be individualized to each patient. This recommendation is congruent with the opinion of an expert physician in the rehabilitation field.
- Higher-quality research involving larger sample sizes and randomized-controlled, double-blinded, placebo-controlled design should be conducted involving the use of amantadine on cognitive function in patients with TBI.

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