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Effectiveness of Amantadine Hydrochloride in the Reduction of Chronic Traumatic Brain Injury Irritability and Aggression

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Background: Following traumatic brain injury (TBI), individuals may experience chronic problems with irritability or aggression, which may need treatment to minimize the negative impact on their relationships, home life, social interactions, community participation, and employment. **Objective:** To test the a priori hypothesis that amantadine reduces irritability (primary hypothesis) and aggression (secondary hypothesis) among individuals greater than 6 months post-TBI. **Methods:** A total of 76 individuals greater than 6 months post-TBI referred for irritability management were enrolled in a parallel-group, randomized, double-blind, placebo-controlled trial of amantadine ($n = 38$) versus placebo ($n = 38$). Study participants were randomly assigned to receive amantadine hydrochloride 100 mg twice daily versus equivalent placebo for 28 days. Symptoms of irritability and aggression were measured before and after treatment using the Neuropsychiatric Inventory Irritability (NPI-I) and Aggression (NPI-A) domains, as well as the NPI-Distress for these domains. **Results:** In the amantadine group, 80.56% improved at least 3 points on the NPI-I, compared with 44.44% in the group that received placebo ($P = .0016$). Mean change in NPI-I was −4.3 in the amantadine group and −2.6 in the placebo group ($P = .0085$). When excluding individuals with minimal to no baseline aggression, mean change in NPI-A was −4.56 in the amantadine group and −2.46 in the placebo group ($P = .046$). Mean changes in NPI-I and NPI-A Distress were not statistically significant between the amantadine and placebo groups. Adverse event occurrence did not differ between the 2 groups. **Conclusions:** Amantadine 100 mg every morning and at noon appears an effective and safe means of reducing frequency and severity of irritability and aggression among individuals with TBI and sufficient creatinine clearance. **Key words:** *aggression*, *agitation*, *amantadine*, *brain injuries*, *dopamine*, *irritability*

IRRITABILITY AND AGGRESSION are present in 29% to 73% of individuals with traumatic brain injury (TBI) and are often chronic and pervasive, contributing to social isolation, care burden, disrupted interpersonal relationships, and incomplete community integration.[1–3] Management with pharmacologic agents is a logical approach, although few studies have studied treatments with adequate rigor to guide medical management.

The mechanisms of TBI-related irritability and aggression have not yet been established. Models exist for *non–TBI*-related aggression that suggest that triggers may exist with any alteration along the pathways of emotional control that includes a provocative stimulus, sensory processing, cognitive appraisal, limbic drive, and cortical inhibition.[4] Along several aspects of this process, neurotransmitter balance, it is thought, may play a large role. However, the mechanisms of *TBI-related* irritability and aggression, and the efficacy of pharmaceutical agents in treating it, are not well-established. Mechanisms for pharmacologic management of aggression in non-TBI and TBI populations may include improved cognitive processing and suppression of limbic drive through manipulation of neurotransmitter availability and function, among other possible mechanisms.

Four randomized controlled medication trials have focused on treating chronic aggression (3 studies of

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β-blockers and one of methylphenidate),[5] which were limited by small sample size, short treatment duration, mixed brain injury etiology, and other study design issues. An evidence-based review on the pharmacologic treatment of TBI aggression published[6] in 2006 found insufficient evidence for standards, guideline-level evidence supporting β-blockers, and option-level evidence for methylphenidate, serotonin-reuptake inhibitors, valproate, lithium, tricyclic antidepressants, and buspirone.

The dopaminergic agent, amantadine, has unknown potential in treating TBI-related irritability and aggression due to a lack of research. Amantadine is reasonably safe, inexpensive, and nonsedating. Therapeutic dosing and effect are achieved rapidly, and nonresponse to the drug can be determined quickly.[7] Amantadine has been used "off-label" for decades to treat a variety of brain injury–related problems and similar problems in other populations. However, existing evidence does not allow us to establish its efficacy for these purposes. The sparse literature of amantadine for treating TBI-related behaviors and cognition[8–13] is summarized (see Table 1). There have been no randomized, placebo-controlled studies published that specifically assess treatment of chronic irritability or aggression in TBI with amantadine.

Amantadine impacts dopaminergic function, acts as a *N*-methyl-D-aspartate channel antagonist, and may impact serotonergic function. Its pleiotropic nature may make this medication ideal for the treatment of a diffuse disease process such as TBI. Theoretical rationale exists for using monoaminergic agents in the management of TBI behaviors,[7,14] such as irritability. Animal[15–18] and clinical TBI studies[7,9,10,19–21] have shown beneficial responses to monoaminergic

TABLE 1 *Published evidence of amantadine effect for improving TBI behaviors*

Author	*N*	Time postinjury	Daily dose	Design	Results and comments
Beers et al[8]	27	Postacute	150-200 mg	Randomized-controlled trial	Behavior improved in the amantadine group Amantadine vs usual care Not blinded Pediatric sample
Chandler et al[9]	2	Acute	400 mg	Case series	Agitation decreased in both subjects
Gualtieri[10]	30	2-144 months	50-400 mg	Case series	19 (63%) responded (reduced agitation, aggression, distractibility, mood swings); 5 (2%) partially responded; no control group Ages 5-59 years
Nichels et al[11]	12	Acute	200-400 mg	Retrospective	10 of 12 improved motor and/or cognitive function (focused and sustained attention, concentration, orientation, alertness, arousal, processing time, psychomotor speed, mobility, vocalization, agitation, anxiety, and participation). No response on depression or sexual inappropriateness
Schneider et al[12]	10	Acute Inpatient rehab	100-300 mg	A-B-A design	No significant difference between amantadine and placebo in orientation, attention, executive function; memory; behavior problems. Heterogeneous sample, inadequately powered, numerous outcomes tested.
Van Reekum et al[13]	1	6 months	300 mg	Case study	Improved behavioral rating (apathy, amotivation, slowness, preservation) Double-blind, placebo-controlled case study

Abbreviation: TBI, traumatic brain injury.

agents and chronically reduced dopamine levels.[22,23] Dopamine is involved in frontal lobe function, behavior, and mood control. Amantadine acts presynaptically (indirectly) to enhance dopamine release and postsynaptically (directly) to inhibit dopamine reuptake.[22–28] When ingested chronically, amantadine enhances the density of postsynaptic dopaminergic receptors and may alter the receptor configuration.[23] In animal models, amantadine appears to competitively block the receptor effects of apomorphine and amphetamine.[29] Amantadine's dopaminergic properties may not be the only means for its behavioral effects. Amantadine also acts as a *N*-methyl-D-aspartate channel blocker, thus decreasing the activation of glutamate,[25] and laboratory evidence suggests that agents regulating glutaminergic function can reverse deficits in learning, memory, and behavior.[30,31] Amantadine's serotonergic function may also impact behavior and mood regulation.[32] Finally, amantadine has been shown to enhance gene expression of brain-derived neurotrophic factor in rodents; thus, it may enhance neuronal growth and function.[33,34]

Behavioral toxicity has been noted with high amantadine dosing (>200 mg). Gualtieri et al[19] reported that for doses up to 400 mg/day, adverse effects included *irritability*, rigidity, depression, lethargy, pedal edema, seizures, hyperactivity, ataxia, and nausea. Adverse effects occurred with higher dosing and resolved with returning to the previously effective dose or discontinuing the medication. Thus, more moderate dosing may be important when used for irritability and aggression.

The dosing of amantadine, as well as its efficacy, for the treatment of TBI behaviors such as irritability needs to be established. This study aims to begin to address the gap in the current knowledge base by conducting a single-center, prospective, double-blind, randomized, placebo-controlled trial to determine the safety and efficacy of moderate-dose amantadine hydrochloride in reducing the severity, frequency, and distress of chronic irritability and aggression following TBI. We hypothesized that 28 days of treatment with amantadine (100 mg every morning and noon), as compared with placebo, administered to individuals with chronic irritability following TBI (at least 6 months postinjury at the time of enrollment), would result in reduced irritability frequency and severity (as measured by the Neuropsychiatric Inventory [NPI]-Irritability domain) at the end of the treatment interval. Secondarily, we hypothesized that amantadine would also reduce (1) observer distress over irritability and (2) frequency, severity, and observer distress over aggression among individuals with TBI. This study also gathered pilot data on participant characteristics to assess their relationship with positive responses to amantadine.

METHODS

Setting

The study was conducted at Carolinas Rehabilitation in Charlotte, North Carolina, approved by Carolinas Medical Center Institutional Review Board and registered on www.clinicaltrials.org (Identifier # NCT00627250; http://clinicaltrials.gov/ct2/show/NCT00627250). Participant recruitment occurred via outpatient referrals from local clinicians, letters from physicians, newsletters, and local brain injury support groups.

Participants

Individuals were eligible for the study if they were 16 to 65 years old and had sustained a closed head injury due to trauma at least 6 months prior to enrollment with a score greater than 2 on NPI-Irritability domain. Enrollment was contingent upon medical and neurological stability, the ability to give informed consent and comply with study protocol, a negative pregnancy test, and creatinine clearance greater than 60 mg/dL. Exclusion criteria included anticipated surgery or medication change during the study, diagnosis of other neurologic disorder, seizure in the month prior to enrollment, concomitant use of neuroleptic agents or monoamine oxidase inhibitors, previous allergy or adverse reaction to amantadine, and ingestion of amantadine in the month prior to study enrollment. Participants were required to have an "observer," defined as a close family member or friend living with them, who was willing and able to observe the presence of irritability. Of note, all psychoactive medications must have been on stable dosing for greater than 1 month prior to enrollment with no plans to start or change such medications during study participation. All rehabilitation therapies and behavior or counseling-based therapies received had to be in existence for greater than 1 month prior to enrollment and expected to continue throughout the study or could not be started during the study.

Study design

Eligible participants were randomized to receive either amantadine hydrochloride 100 mg every morning and noon or matched placebo for 28 days (±3 days) using blocked randomization with stratification for depression (<13 vs ≥13 on the Beck Depression Inventory–II [BDI-II]) and prior exposure to amantadine (past amantadine exposure vs drug-naive).

Procedures

Demographic variables were collected via interview at the time of study enrollment. Medical history,

psychiatric history, injury severity data, and cause of injury were collected during interview and verified via medical chart review. Assessment measures were administered to the participant's observer. Observer ratings were chosen in favor of self-ratings due to decreased self-awareness in TBI, particularly for emotional, behavioral, and cognitive deficits. The participant completed the Global Mental Health Scale, Fatigue Impact Scale (FIS), Brief Symptom Inventory (BSI), and BDI-II. Once the baseline assessments were completed and eligibility criteria confirmed, the participant was randomized and the study medication dispensed. Participants were called on days 4 and 14 to assess tolerance and encourage compliance. The protocol allowed for dose reduction or drug termination if needed. The participant and the observer returned 28 days after beginning study treatment to repeat assessment measures. Adverse events, changes in concomitant medications, and the remaining number of pills were recorded. An adverse event was any unfavorable and unintended diagnosis, sign (including an abnormal laboratory finding), symptom, or disease that occurred during study participation, whether or not related to the intervention. Adverse events include new events not present during the preintervention period or events that were present during the preintervention period but increased in severity during study participation. Medication compliance was defined as taking 80% or more of the study medication. Outcome assessment at 28 days was chosen to allow adequate time to observe any changes in the individual's irritability and aggression, and to accommodate the 4-week observation interval of the NPI. At the end of the 28-day study period, participants were provided a 30-day trial of amantadine. No efficacy assessment of this open-label use was performed.

Randomization and masking

Treatment group assignment occurred through computer-generated block randomization. Everyone except the central pharmacist was blinded to group assignment.

Measures

NPI-Irritability and aggression domains

The NPI is a 40-item tool developed to assess 12 behavioral domains in dementia and has been used in TBI populations.[9,10,35] For each domain, several questions are asked about the behavior. The most problematic item detected through the questions is graded for severity (1 = mild, 2 = moderate, 3 = severe) and frequency ranging from 1 to 4, with 4 representing the highest frequency. The product of the severity and frequency of the most problematic item are calculated for each behavioral domain (range, 0-12). This is rated by the observer about the study participant. Distress over the most problematic item in each domain is also assessed and referred to as NPI-D or NPI Distress. The informant rates the emotional distress they themselves experience in relation to that domain expressed by the participant on a 6-point scale (range, 0-5), with lower scores indicating minimal distress. For this study, only the NPI Irritability and the Agitation/Aggression domains were scored by the informant. The NPI-I domain assesses bad temper, rapid mood changes, sudden anger, impatience, crankiness, and argumentative. The NPI-A domain assesses the tendency to get upset, resistance to activities, stubbornness, uncooperativeness, shouting, cursing, and physical behaviors indicative of aggression.

The NPI has established content and concurrent validity, as well as between-rater (approximately 95% for both frequency and severity), test-retest (0.79 for frequency and 0.86 for severity), and internal consistency reliability (the Cronbach alpha of 0.88).[36] The NPI-D has established content and concurrent validity, between-rater (0.96), test-retest (0.92), and internal consistency.[37]

Beck's depression inventory–II

The BDI-II[38] is a 21-item self-report instrument used to assess depression symptomatology and severity with established reliability and construct validity.[38] Items are rated on a 4-point scale ranging from 0 to 3. Ratings for the 21 items are summed with a maximum total score of 63. For this study, the BDI-II was administered to the subject only.

Brief symptom inventory

This 18-item self-report instrument[39] quantifies psychological distress. Frequency ratings are added to yield scores for somatization, depression, and anxiety and T-scores derived on the basis of community norms. Only the BSI Anxiety subscore was used.

Global mental health scale

This 9-item, 6-point Likert scale assesses self-rated affect and anxiety over the past month, with the sensitivity to detect most DSM (Diagnostic and Statistical Manual of Mental) disorders.[40,41] Both participant and observer completed the measure about the participant.

Fatigue impact scale

This 20-item questionnaire assesses cognitive, physical, and social dimensions using a 5-point Likert Scale. High internal consistency has been reported.[42] Compared to the Visual Analog Scale for Fatigue and Fatigue

Severity Scale, FIS provides a more comprehensive examination of fatigue in TBI.[43] The FIS was administered to the participant.

Statistical methods

Analyses were performed using SAS (Cary, North Carolina). The principal intent-to-treat analysis compared the percentage of participants who demonstrated a meaningful change in irritability from baseline to 28 days, as defined a priori as a decrease of at least 3 points in the NPI-I score (frequency × severity). This cut point was selected to capture a clinically meaningful change and was based on input from people with brain injury, their family members, and clinicians. Scores between the amantadine and placebo groups were analyzed using the chi-square test. The percentage of adverse effects were compared between the 2 groups using the chi-square/Fischer exact test. These tests were also used for all data measured on the nominal scale (eg, gender). Results that were ordinal or not normally distributed were tested with the Wilcoxon rank sum test.

Additional planned analyses included comparisons between the amantadine and placebo group on mean change in the NPI-I score (frequency × severity) from baseline to 28 days; mean change in the NPI-I Distress score from baseline to 28 days; mean change in the NPI-A score (frequency × severity) and NPI-A Distress score from baseline to 28 days; and adverse event occurrence between the treatment groups. The Spearman correlations were performed to assess the characteristics associated with improvement in irritability in the amantadine group.

It was determined a priori that the primary aggression analysis would be performed with exclusion of any participants with NPI-A score 0 to 2 to ensure that the analysis included individuals with aggression and to be consistent with the eligibility criteria for the presence of irritability (NPI-I > 2). The analysis was also performed with the entire sample to check for potential worsening of those with minimal to no aggression on amantadine.

The sample size is based on performing a chi-square test. An a priori calculation indicated that a sample size of 66 would be needed for the principal analysis to detect a difference of 20% having a successful decrease in irritability in the placebo group versus 55% in the amantadine group, assuming 80% power and alpha at 0.05. Oversampling of 10 participants was conducted to allow for up to 15% loss to follow-up.

RESULTS

Participants

Eighty-four individuals were screened for inclusion, and 76 ultimately enrolled and randomized (38 in each group) (see the Figure). All but 4 (2 placebo and 2 amantadine) completed the study. No unblinding of the participant assignment to the participants, investigators, or other study staff (as might be needed in medical emergency or other reason) occurred. The amantadine and placebo groups were well matched with respect to baseline factors (see Table 2). There was a statistically significant difference between the mean age of the 2 groups, but age was not related to outcome. Ninety-two percent in both groups (70 out of 76) took greater than 80% of the medication. Mean compliance between the treatment groups was not statistically significant with a mean of 93% compliance in the amantadine group and 90% in the placebo group.

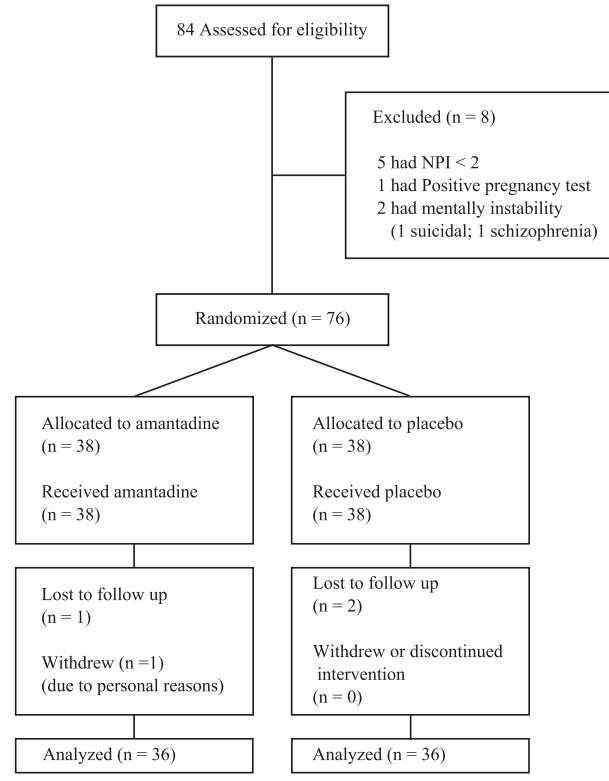

Figure. Consort diagram of study participation.

Although the presence of irritability was required for enrollment, aggression and observer distress over irritability or aggression were not mandates. All study participants had a baseline NPI-Irritability Distress score of greater than 0 with 10 participants rating 1 or 2. One participant had a 0 baseline NPI-Aggression score, and 17 scored 1 or 2. On NPI-Aggression Distress, 1 participant scored 0 and 25 scored 1 or 2 at baseline.

Amantadine effect on irritability

Responses to treatment are outlined (see Table 3). In the amantadine group, 80.56% improved at least 3 points on the NPI-I, compared with 44.44% in

TABLE 2 *Baseline participant characteristics*

	Amantadine group ($N = 38$), n (%)	Placebo group ($N = 38$), n (%)
Gender		
Male	25 (65.79%)	22 (57.89%)
Female	13 (34.21%)	16 (42.11%)
Ethnicity		
White	34 (89.47%)	31 (81.58%)
African American	4 (10.53%)	6 (15.79%)
Other	0 (0%)	1 (2.63)
Cause of injury		
Vehicular	24 (63.15%)	23 (60.53%)
Assault	1 (2.63%)	1 (2.63%)
Fall	5 (13.16%)	4 (10.53%)
Sports	0 (0%)	1 (2.63%)
Pedestrian	5 (13.16%)	4 (10.53%)
Other	3 (7.89%)	5 (13.16%)
	Mean (SD)	**Mean (SD)**
Age at enrollment,[a] y	34.7 (±13.2)	42.1 (±13.7)
Age at injury,[a] y	29.4 (±12.7)	34.7 (±13.2)
Time since injury, y	5.3 (±6)	4.7 (±4.2)
Glasgow Coma Scale	9.5 (±4.4); $N = 11$	7.5 (±5.1); $N = 17$
NPI-Irritability	7.2 (±3.0)	6.6 (±2.7)
NPI-Irritability Distress	17.6 (±7.1)	13.9 (±6.8)
NPI-Aggression	5.2 (±3.4)	5.2 (±3.2)
NPI-Aggression Distress	10.6 (±8.0)	8.6 (±5.2)
Beck's Depression Inventory–II	24 (±13.2)	22.8 (±11.9)
Brief Symptom Inventory–Anxiety	1.2 (±1.0)	1.1 (±1.0)
Fatigue Impact Scale	66.2 (±41.4)	66.2 (±41.6)
Global Mental Health Scale	34.6 (±8.7)	32.9 (±7.7)

Abbreviation: NPI, Neuropsychiatric Inventory Irritability.
[a]Age at injury and age at enrollment between the 2 groups were statistically significant but were not related to outcome.

the placebo group. Mean change in NPI-I score was −4.3 in the amantadine group, compared with −2.6 in the placebo group ($P = .0085$). The mean change in both the *frequency* and the *severity* of irritability (most problematic frequency and severity items) were statistically significant between the amantadine and placebo groups ($P = .0156$ and $P = .0055$, respectively). Mean change in NPI-I Distress was not statistically significant as indicated in Table 3. There were no statistically significant differences in the change in BDI-II, Global Mental Health Scale, or BSI-Anxiety scores between the amantadine and placebo groups.

TABLE 3 *Intention-to-treat analyses of irritability*

Treatment group	NPI Irritability ≥ 2-Point change (primary analysis)	Mean change in NPI irritability	Mean change in NPI- irritability distress
Amantadine	81%	−4.3	−7.6
Placebo	44%	−2.6	−5.8
P	.0016[a]	.0085[a]	.2521

Abbreviation: NPI, Neuropsychiatric Inventory Irritability.
[a]Statistically significant.

Amantadine effect on aggression

The mean change in aggression scores (NPI-A and NPI-A Distress) were not statistically significant in the amantadine group, as compared with the placebo group when including all of the study participants. When the 18 individuals with baseline NPI-A scores of 0 to 2 were excluded, mean change in NPI-A was statistically significant between the amantadine and placebo groups ($P = .046$). Mean and median changes in NPI-A were −4.65 and −6, respectively, for the amantadine group, compared with mean change of −2.46 and median change of −3 median for the placebo group.

Adverse events

Amantadine was well tolerated among study participants. There were few adverse events and no significant difference between the 2 groups on withdrawals or adverse events (Table 4). One participant required study drug termination, secondary to a seizure. No dose reductions were required.

DISCUSSION

The study revealed statistically significant improvement in moderate to severe irritability and aggression between the amantadine and placebo groups. The efficacy of amantadine in reducing the frequency and severity of irritability has direct clinical relevance due to the pervasive impact of irritability on functionality and relationships. Exposure to amantadine did not appear to increase the risk of adverse medical, neurologic, or behavioral effects, indicating that it can be used safely at moderate doses of 200 mg daily in individuals with TBI who have sufficient renal clearance (>60 mg/dL creatinine clearance was required for this study). No significant reduction in NPI observer distress (NPI-Distress) was noted. This is the first study looking specifically at the effect of amantadine on chronic irritability and aggression due to TBI. The rigorous, randomized, double-blind, placebo-controlled design provides strong support of the potential use of amantadine for this purpose. Further research should replicate the study to confirm reproducibility of amantadine's positive effect on irritability and aggression. Replication with a larger sample size would allow exploration of the characteristics of positive and negative responders and a more adequately powered assessment the effect of amantadine on observer distress.

Amantadine may improve irritability and aggression through enhancing cognitive function and, through this mechanism, may enhance cognitive appraisal and behavioral dysinhibition. While a number of clinicians hold the opinion that amantadine is helpful in treating persons with TBI who have cognitive impairment in the postacute period, there is limited empirical support for this proposition.[6,8,12,25,28,44–47] Frontotemporal and brainstem damage commonly occur with TBI with associated deficits in motor control, expressive language, regulation (orbitofrontal), executive behavior (frontal convexity), initiation, and arousal. Within the brainstem lie the primary cell bodies for the monoaminergic system[44,47] with striatocortical projections.[46] This dopaminergic system impacts behavior, motor control, autonomic function, and arousal.[48] Kraus et al[25] administered neuropsychological tests and positron emission tomography to 22 individuals with TBI taking amantadine 400 mg daily and found a significant increase in left prefrontal cortex glucose metabolism, which was significantly correlated with executive domain scores. Further research is needed to explore the cognitive effects of amantadine, and whether amantadine's effect on cognitive function plays a role in reducing irritability and aggression.

The use of a double-blind, placebo-controlled methodology was critical to addressing the research question. Although a large difference was found between the 2 groups, a large placebo effect was observed in this

TABLE 4 *Number of participants that experienced adverse events*

Adverse event	Amantadine, *N*	Placebo, *N*	*P*[a]	*P*[b]
Any adverse event	19 (50%)	17 (45%)	.637	. . .
Tremors and shakes	2 (5%)	4 (11%)	.674	.398
Change in appetite	4 (11%)	2 (5%)	.674	.452
Gastrointestinal	3 (8%)	2 (5%)	1.000	.701
Aches and pains	4 (11%)	1 (3%)	.357	.701
Sexual problems	0 (0%)	3 (8%)	.239	.079
Disoriented	2 (5%)	2 (5%)	1.000	.977
Seizure	1 (3%)	0 (0%)	1.000	.984

[a] *P* value from the chi-square test or the Fisher exact test comparing difference in proportions.
[b] *P* value from the Wilcoxon rank sum test using ordinal scale to measure severity of event.

study. Placebo effect may, in part, result from the dependence on subjective observer reporting and observer bias. Such placebo effect is known to be common with studies of subjective measure of emotional issues without a direct physiologic effect.[49,50] Placebo effect has also been found to be associated with the production of endorphins and dopamine,[50] which could potentially impact irritability and aggression. Positive change in the placebo group may also reflect variability in the outcome measure ratings or the inconsistency in baseline behavior from month to month.

Caution should be used when interpreting the nonsignificant findings on Distress, as the study was only secondarily designed to assess this. With no inclusion criteria for distress, some enrolled did not have marked distress at baseline. The study required close enough proximity to observe the study participant's behaviors but did not require that the observer have a caregiving role or bear the brunt of the irritability behaviors. Thus, observers represented a variety of different roles and relationships to the person with brain injury, not all observers served a heavy caregiving role. The impact of amantadine on distress is not clear from this study. Future studies are needed to specifically look at distress, its relationship to behavior, and its response to treatment.

A few limitations should be considered. First, the study used subjective measures as irritability and aggression generally expresses itself sporadically in the home setting, which would preclude the use of more objective measures. Thus, the study findings are subject to observer bias. Second, the study was not powered to answer questions about what characteristics of individuals with irritability secondary to TBI would be most likely benefit from amantadine, or to explore the mechanism of the beneficial effect. Third, the study centered on *chronic* irritability and may not extrapolate to behaviors during the acute period after TBI.

CONCLUSION

Amantadine 200 mg daily appears a safe and effective means of reducing irritability and aggression among individuals with TBI greater than 6 months' duration and sufficient creatinine clearance.

REFERENCES

1. Hammond FM, Davis CS, Whiteside YO, Philbrick P, Hirsch MA. Marital adjustment and stability following traumatic brain injury: a pilot qualitative analysis of spouse perspectives. *J Head Trauma Rehabil.* 2011;26(1):69–78.
2. Kilmer RP, Demakis GJ, Hammond FM, et al. Use of the Neuropsychiatric Inventory in traumatic brain injury: a pilot investigation. *Rehabil Psychol.* 2006;51:232–238.
3. Ciurli P, Formisano R, Bivona U, et al. Neuropsychiatric disorders in persons with severe traumatic brain injury: prevalence, phenomenology, and relationship with demographic, clinical, and functional features. *J Head Trauma Rehabil.* 2011;26(2):116–126.
4. Siever LJ. Neurobiology of aggression and violence. *Am J Psychiatry*. 2008;165:429–442.
5. Fleminger S, Greenwood RJ, Oliver DL. Pharmacological management for agitation and aggression in people with acquired brain injury. *Cochrane Database Syst Rev.* 2003:CD003299. doi: 10.1002/14651858.CD003299.
6. Warden DL, Gordon B, McAllister TW, et al. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. *J Neurotrauma.* 2006;23(10):1468–1501.
7. Gualtieri T, Chandler M, Coons TB, Brown LT. Amantadine: a new clinical profile for traumatic brain injury [Review]. *Clin Neuropharmacol.* 1989;12:(4)258–270.
8. Beers SR, Skold A, Dixon CE, Adelson PD. Neurobehavioral effects of amantadine after pediatric traumatic brain injury: a preliminary report. *J Head Trauma Rehabil.* 2005;20(5):450–463.
9. Chandler MC, Barnhill JL, Gualtieri CT. Amantadine for the agitated head-injury patient. *Brain Inj.* 1988;2:(4)309–311.
10. Gualtieri CT. *Neuropsychiatry and Behavioral Pharmacology*. New York: Springer-Verlag; 1991.
11. Nichels JL, Schneider WN, Dombovy ML, Wong TM. Clinical use of amantadine in brain injury and rehabilitation. *Brain Inj.* 1994;8(8):709–718.
12. Schneider WN, Drew-Cates J, Wong TM, et al. Cognitive and behavioral efficacy of amantadine in acute trauma brain injury: an initial double-blind placebo-controlled study. *Brain Inj.* 1999;13(11):863–872.
13. Van Reekum R, Bayley M, Garner S, et al. N of 1 study: amantadine for the amotivational syndrome in a patient with traumatic brain injury. *Brain Inj.* 1995;9(1):49–53.
14. Levin H, Kraus MF. The frontal lobes and traumatic brain injury. *J Neuropsychiatry Clin Neurosci.* 1994;6:443–454.
15. Feeney DM, Gonzalez A, Law WA. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex surgery. *Science.* 1982;217:855–857.
16. Kasamatusu T, Pettigrew JK, Ary M. Cortical recovery from effects of monocular deprivation: acceleration with norepinephrine and suppression with 6-hydroxydopamine. *J Neurophysiol.* 1981;45:139–162.
17. Kasamatusu T, Pettigrew JD. Preservation of binocularity after monocular deprivation in the striate cortex of kittens treated with 6-hydroxydopamine. *J Comp Neurol.* 1979;185:139–162.
18. Feeney DM, Weisend MP, Kline AE. Noradrenergic pharmacotherapy, intracerebral infusion and adrenal transplantation promote functional recovery after cortical damage. *J Neural Transplant Plast.* 1993;4(3):199–213.
19. Gualtieri CT, Evans RW. Stimulant treatment for the neurobehavioral sequelae of traumatic brain injury. *Brain Inj.* 1988;2(4):273–290.
20. Andersson S, Berslad J, Finset A, Grimsmo J. Amantadine in cognitive failure in patients with traumatic brain injury. *Tidsskrift den Norske Laegeforening.* 1992;112:2070–2072.
21. Zafonte RD, Watanabe T, Mann N. Amantadine: a potential treatment for the minimally conscious state. *Brain Inj.* 1998;12(7):617–621.
22. Aokl F, Sitar D. Clinical pharmacokinetics of amantadine hydrochloride. *Clin Pharmacokinet.* 1988;14:35–51.
23. Peeters M, Maloteaux JM, Hermans E. Distinct effects of amantadine and memantine on dopaminergic transmission in the rat striatum. *Neurosci Lett.* 2003;343:205–209.

24. Gianutsos G, Stewart C, Dunn JP. Pharmacological changes in dopaminergic systems induced by long-term administration of amantadine. *Eur J Pharmacol*. 1985;110:357–361.
25. Kraus M, Smith G, Butters M, et al. Effects of the dopaminergic agents and NMDA receptor antagonist amantadine on cognitive function, cerebral glucose metabolism and D2 receptor availability in chronic traumatic brain injury: a study using positron emission tomography. *Brain Inj*. 2005;19:471–479.
26. Werling LL, Keller A, Frank J, Nuwayhid S. A comparison of the binding profiles of dextromethorphan, memantine, fluoxetine and amitriptyline: treatment of involuntary emotional expression disorder. *Exp Neurol*. 2007;207:248–257.
27. Moresco R, Volonte M, Meesa C, et al. New perspectives on neurochemical effects of amantadine in the brain of Parkinson's patients: a PET raclopride study. *J Neural Transmission*. 2002;109:1265–1274.
28. Sawyer E, Mauro L, Ohlinger M. Amantadine enhancement of arousal and cognition after traumatic brain injury. *Ann Pharmacother*. 2008;42:247–251.
29. Allen R. Role of amantadine in the management of neuroleptic-induced extrapyramidal syndromes: overview and pharmacology. *Clin Neuropharmacol*. 1983;6(suppl 1):S64–S73.
30. Evans S, Levin F, Brooks D, Garawi F. A pilot double blind treatment trial of memantine for alcohol dependence. *Alcohol Clin Exp Res*. 2007;31:775–782.
31. Parsons C, Stoffler A, Danysz W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system–too little activation is bad, too much is even worse. *Neuropharmacology*. 2007;53:699–723.
32. Glennon R, Young R. MDMA stimulus generalization to the 5HT1a serotonin agonist 8-hydroxyl (di-*n*-propylamino) tetralin. *Pharmacol Biochem Behav*. 2000;66:483–488.
33. Rogoz Z, Skuza G, Legutko B. Repeated cotreatment with imipramine and amantadine induces hippocampal brain derived neurotrophic factor gene expression in rats. *J Physiol Pharmacol*. 2007;58:219–234.
34. Caumont A, Octave J, Hermans E. Amantadine and memantine induce the expression of the glial cell line derived neurotrophic factor in C6 glioma cells. *Neurosci Lett*. 2006;394:196–201.
35. Hammond F, Bickett-Knotts A, Hirsch M, et al. Posttraumatic irritability and related factors. *J Head Trauma Rehabil*. 2006;21(5):412–413.
36. Cummings JL, Mega MS, Gray K, et al. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308–2314.
37. Kaufer DI, Cummings JL, Christine D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. *J Am Geriatr Soc*. 1998;46(2):210–215.
38. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory–II*. San Antonio, TX: Psychological Corporation; 1996.
39. Derogatis LR. *BSI 18. Brief Symptom Inventory 18*. Minneapolis, MN: NCS Pearson; 2000.
40. Wyman PA, Cowen EL, Work WC, et al. Developmental and caregiving factors differentiating parents of young stress-affected and stress-resilient urban children: a replication and extension. *Child Dev*. 1999;70:645–659.
41. Berwick DM, Murphy JM, Goldman PA, et al. Performance of a 5-item mental health screening test. *Med Care*. 1991;29(2):87–178.
42. LaChapelle DL, Frasquillo F. An evaluation of subjective and objective measures of fatigue in patients with brain injury and healthy controls. *Brain Inj*. 1998;12(8):649–659.
43. Fisk JD, Ritvo PF, Ross L, et al. Measuring the functional impact of fatigue: initial validation of the Fatigue Impact Scale. *Clin Infect Dis* 1994;18(suppl 1):S79–S83.
44. Kraus MF, Maki PM. Effect of amantadine hydrochloride on symptoms of frontal lobe dysfunction in brain injury: case studies and review. *J Neuropsychiatry Clin Neurosci*. 1997;9(2):222–230.
45. Leone H, Polsonetti BW. Amantadine for traumatic brain injury: does it improve cognition and reduce agitation? *J Clin Pharm Ther*. 2005;30:101–104.
46. Tenovuo O. Pharmacological enhancement of cognitive and behavioral deficits after traumatic brain injury. *Cur Opin Neurol*. 2006;19:528–533.
47. Zasler N. Advances in neuropharmacological rehabilitation for brain dysfunction. *Brain Inj*. 1992;6:1–14.
48. Bradley PB. *Introduction to Neuropharmacology*. London: Wright Publishing Company; 1989.
49. Wechsler ME, Kelle JM, Boyd IOE, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *NEJM*. 2011;365:119–126.
50. Putting the placebo effect to work. *Harvard Letter*. http://www.health.harvard.edu/newsletters/Harvard_Health_Letter/2012/April/putting-the-placebo-effect-to-work. Published 2012. Accessed October 23, 2013.