**Title:**

Potential Impact of Amantadine on Aggression in Chronic Traumatic Brain Injury

Flora M. Hammond; James F. Malec; Ross D. Zafonte; Mark Sherer; Jennifer Bogner; Sureyya Dikmen; Marybeth P. Whitney; Kathleen R. Bell; Susan M. Perkins; Elizabeth A. Moser

**ABSTRACT:**

**Objective:** To assess the effects of amantadine on anger and aggression among individuals with a chronic traumatic brain injury (TBI).

**Methods:** A cohort of 118 persons with chronic TBI (> 6 months post-injury) and moderate-severe aggression selected from a larger cohort of 168 participants enrolled in a parallel-group, randomized, double-blind, placebo-controlled trial of amantadine 100 mg twice daily (n=82) vs placebo (n=86) for treatment of irritability were studied. Anger and aggression were measured at treatment days 0, 28 and 60 using observer-rated and participant-rated State Trait Anger Expression Inventory-2 (STAXI-2) and Neuropsychiatric Inventory Agitation/Aggression Domain (NPI-A) Most Problematic and Distress scores.

**Results:** Participant-rated Day-60 NPI-A Most Problematic (adjusted p = 0.0118) and NPI-A Distress (adjusted p = 0.0118) were statistically significant between the two groups, but STAXI-2 differences were not significant after adjustment for multiple comparisons. Substantial improvements were noted in both amantadine and placebo groups (70% vs. 56% improving at least 3 points on Day 60 Observer NPI-A; p=0.11).

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**Conclusion:** Amantadine 100 mg twice daily in this population with chronic TBI appears to be beneficial in decreasing aggression from the perspective of the individual with TBI. No beneficial impact on anger was found.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00779324; http://www.clinicaltrials.gov/ct2/show/NCT00779324?term=irritability&rank=6

**Key Words:** Brain Injuries, Aggression, Anger, Amantadine

## INTRODUCTION

Anger and aggression are among the more common manifestations of affective and behavioral dysregulation observed following traumatic brain injury (TBI).[1-3] Aggression has been observed in approximately 25-73% of individuals with chronic TBI.[1,2,4] Compared to uninjured age, gender, and education-matched peers, after moderate-severe TBI excessive anger occurs in 39% (compared to 20%) and verbal aggression in 41% (compared to 18%).[5] While in an angry or aggressive state, interpersonal communication is often non-adaptive and information processing inefficient resulting in poorer rehabilitation outcomes, exclusion from rehabilitation services due to safety concerns, social isolation, interpersonal and relationship stresses and losses, caregiver burden, criminal behavior, inability to live at home, and employment challenges. [2]

Despite the substantial impact, systematic reviews have revealed minimal evidence for efficacious pharmacologic treatment of aggression and anger after TBI.[6,7] Arciniegas et al.[3] suggested the agents most likely to be effective are those that enhance the function of neural circuitry facilitating top-down regulation of behavior, assuming that these areas are relatively preserved post-TBI. However, when prefrontal areas are not intact, targeting the limbic catecholaminergic functions directly may be a logical option. For example, amantadine is a pleotropic agent with indirect pre-synaptic and direct post-synaptic dopaminergic effects, N-methyl-D-aspartate channel antagonism, and serotonergic effects that may influence top-down regulation through enhanced cognitive appraisal and behavioral disinhibition.

Preliminary evidence suggest amantadine may reduce TBI related aggression.

Hammond et al.[8] enrolled 76 individuals with chronic TBI (> 6 months post-injury) and associated irritability into a single-site, randomized, controlled trial of amantadine 100mg twice daily versus placebo for 28 days. For those with aggression at baseline (n=68), the amantadine group experienced significantly greater improvement than the placebo group on observer-rated Neuropsychiatric Inventory Aggression (NPI-A) using the item rated as most problematic. In the amantadine group, NPI-A Most Problematic mean change was -4.56 compared to -2.46 in the placebo group (p=0.046). This study assessed only an observer‘s perspective (an observer was someone close enough to the person with brain injury to have regular interactions and witness behaviors). Observer distress regarding aggression did not differ significantly between the two arms. Some observers did not have considerable distress at baseline.

The study was replicated with a larger, multi-site sample using both observer and participant perspectives of irritability, aggression, and anger. For the irritability outcome, Hammond et al.[9] found observer ratings between the two groups were not statistically significantly different at Day 28 or 60; however, the majority in both groups had improved at both assessments compared to baseline. While the result of this study of amantadine 100 mg every morning and noon to reduce irritability was not positive from the Observer perspective, there were indications of improvement in irritability at day 60 from the perspective of persons with TBI and clinicians that may warrant further investigation.

The present study aims to study the effect of amantadine on aggression and anger in the cohort of participants from the Hammond, et al[9] multi-site, prospective, double-blind, randomized, placebo-controlled trial who had moderate-severe aggression at

baseline. We hypothesized that, compared to placebo, amantadine (100 mg every morning and noon) administered to individuals with aggression (NPI-A Most Problematic $\geq$ 6) following TBI (at least 6 months post-injury), would result in reduced aggression (frequency, severity, and distress) at days 28 and 60 as measured by an observer and the participant with TBI. For purposes of this study we defined aggression as a NPI-A Most Problematic score of at least 6. We also hypothesized that amantadine would result in reduced anger at days 28 and 60 as measured by an observer and the participant with TBI. We measured anger using the State Trait Anger Expression Inventory (STAXI-2). Secondarily we studied the effects of amantadine on the entire cohort to include those with mild or no aggression at baseline (results available in supplemental digital content).

## METHODS

### Setting

Study sites were: Carolinas Rehabilitation in Charlotte, North Carolina (lead site), Indiana University/ Rehabilitation Hospital of Indiana (Indianapolis, IN), Kessler Institute of Rehabilitation (West Orange, New Jersey); Spaulding Rehabilitation Hospital (Boston, MA); TIRR Memorial Hermann (Houston, TX); The Ohio State University (Columbus, OH); University of Washington (Seattle, WA).

### Study Oversight

Each site received Institutional Review Board approval. The study was registered on www.clinicaltrials.org (#NCT00779324). Participants and observers gave their informed

consent. A data coordinating center managed the concealed treatment allocation, data storage, and data monitoring, and upon study closure, transferred the data to the statistician. Independent oversight was provided though an external Data and Safety Monitoring Board

## Participants

Recruitment was through referrals, physician letters, newsletters, and support groups. Eligibility criteria, including presence of TBI, are summarized in Table 1. Most participants lived in the community although this was not required. Study participants were expected to have no anticipated major life events or changes, surgeries, new therapies or changes in medications during the course of the study. We did not attempt to control for or compare groups on environment, medications, therapy involvement, stressors, and other such factors that may impact behavior or potentiate treatment effects since these factors are highly variable. For example, both rehabilitation and psychological therapies may vary considerably in approach and quality among providers and hence there is no accepted method to quantify the impact of these types of therapy. Rather we relied on random assignment to control for this and other extraneous variables between groups. Measures administered to participants as well as an observer. An observer was defined as someone close enough to the person with brain injury to have sufficient interactions to witness the participant's behaviors through out the study.

For the present study of aggression and anger, we a priori planned to analyze two samples: 1) The subset of individuals with moderate or severe aggression (those with

NPI-A Most Problematic <6 were excluded); and 2) The entire sample from the trial for treatment of irritability which included participants with no or mild aggression at baseline. The results of both analyses are included in this manuscript with an emphasis on the analyses of the subset with moderate or severe aggression. The original sample size of 168 was based on the power needed to replicate the study of the effect of amantadine on the primary outcome (irritability) and allow for 8% attrition.[9,10]

## Procedures

Data (demographics, medical history, and injury data) were collected and verified through interview and record review. Measures of participant behavior were administered to the participant and the participant's observer. After confirmation of eligibility and baseline assessment, participants were randomly allocated to take amantadine (100 mg every morning and noon) or placebo equivalent. In cases of presumed drug intolerance, the dose was reduced or terminated per pre-specified protocol. Participants and observers completed the assessment measures at baseline, and treatment day 28 and day 60. Definition of medication compliance was pre-specified as taking at least 80% of the study medication.

## Randomization and Masking

Computer-generated block randomization was performed and concealed group allocation occurred through the study web page managed by the data coordinating center. After the site coordinators entered the participant's eligibility data and eligibility confirmed, the

data coordinating center assigned a study number which indicated which study drug kit to dispense. Randomization was stratified for depression (< 13 vs. ≥ 13 on the Beck Depression Inventory – II) for the trial of amantadine for reduction of irritability. This was done to ensure equal distribution of depression in the amantadine and placebo groups because depression is common after TBI and irritability can be associated with depression. The compounding pharmacist and data coordinating center had access to group assignment, while all study personnel, participants, and observers were blinded to group allocation.

## Measures

The study outcome measures were chosen based on the measures' ability to operationalize the concepts of aggression and anger, and the wide use of these measures in both TBI and dementia literature. The NPI-A has demonstrated sensitivity to changes in aggression in prior medication trials such as Hammond, et al. single site amantadine study.[8]

*NPI – Agitation/Aggression (NPI – A) Most Problematic:* The NPI assesses 12 behavioral domains,[11] including aggression. For this study, only the Irritability domain (administered for eligibility) and Agitation/Aggression domain were administered. The NPI-A domain asks if over the preceding month the individual got upset, resisted activities, shouted, cursed angrily, slammed doors, kicked furniture, threw things, hurt or hit others, or was stubborn, uncooperative or hard to handle. Typical administration has the rater determine the frequency (1-4) and severity (1-3) of the most aberrant of these behavior(s) with the

possibility that this rating will include several relevant items. This is a complex task made more difficult with the memory and executive function deficits accompanying TBI. Thus, we had the raters indicate which of these behaviors were present and which one item was the most problematic. We then had them rate the frequency and severity of that one item, referred to as *Most Problematic*. The domain score is obtained by multiplying the severity and frequency ratings.[11] Consistent with the design of the measure, the NPI was rated by the observer. A version was also developed and used to record participant report.

*NPI-A Distress:* NPI-Distress measures the rater's distress related to the behavior using a 6-point scale.[12] Observers rated the NPI-A Distress about the participant's aggressive behavior, participants rated their distress about their own behavior.

*State Trait Anger Expression Inventory (STAXI-2)*: The STAXI-2,[13] captures the experience and the expression of anger through 57 questions about intensity and frequency using a 4-point Likert scale. STAXI-2 has internal consistency (α coefficient 0.86) [13] and has been used in TBI studies.[14,15] It is comprised of 3 parts: Part 1 (State Anger), Part 2 (Trait Anger), and Part 3 (Anger Expression). The STAXI-2 was administered as designed, to the person expressing the anger (participants). With permission from the measure's author, we modified the tool to capture an external view, and administered to observers.

*Other measures:* To characterize the sample's level of functioning, the Glasgow Outcome Scale-Extended (GOS-E),[16] was collected at baseline as was the Beck Depression Inventory-II.[17] which was used to stratify the sample on depression during randomization.

**Statistical Methods**

Analyses were performed using SAS® 9.4 and were conducted using the intention-to-treat principle. A two-tailed p-value <0.05 was considered statistically significant. The treatment groups were compared on baseline characteristics. For ordinal variables, the normal approximation for the Wilcoxon rank sum test was used. For categorical variables, Chi-square tests or Fisher's exact tests were used.

Pre-specified analyses for the subsample of persons with observer reported moderate to severe aggression (NPI-A ≥ 6) included: 1) Comparison of the change in NPI-A and STAXI-2 scores from baseline to Day 28 and Baseline to Day 60; and 2) Comparison of the percentages of participants who decreased at least 3 points in the NPI-A Most Problematic (a priori definition of meaningful change in aggression). Change in NPI-A Most Problematic (frequency x severity), NPI-A Distress, and STAXI-2 scores (State, Trait, and Anger) from baseline to Day 28 and baseline to Day 60 were compared between the two groups using a Wilcoxon rank sum (Mann-Whitney) test for ordinal data. For analysis of NPI-A Distress, those with no or mild Observer distress (NPI-A Distress scores of 0-2) at baseline were excluded as pre-specified in the protocol. The percentages of participants with decrease in NPI-A of at least 3 points from baseline to 28 days and baseline to Day 60 was compared between the two groups using chi-square or Fisher's exact test. P-values for the Wilcoxon rank sum tests were adjusted for multiple comparisons within the domain of respondent, follow up interval, and instrument (e.g., NPI-A, STAXI) utilizing the Holm's sequential Bonferroni method.[18] As planned, all analyses were repeated on the entire cohort from the irritability trial.

## RESULTS

### Participants

To derive the original cohort, 324 individuals were screened and 168 were enrolled and randomized (86 placebo and 82 amantadine) as previously published.[9] 11 (6.6%) of the participants (4 placebo and 7 amantadine) did not complete the study. Compliance ($\geq$80% prescribed study drug consumed per pill count) was high with 88.5% compliance in amantadine group and 86.9% in placebo group.

Of the cohort of 168 irritability study participants, 118 showed moderate or severe aggression at baseline assessment as indicated by observer reported moderate to severe aggression (NPI-A $\geq$ 6). Of these, 57 were randomized to the placebo control group and 61 were randomized to amantadine. Figure 1 depicts the flow diagram for the aggression subset. Table 2 summarizes the baseline characteristics of the amantadine and placebo groups for the subset with moderate-severe aggression and the entire original group. For both study samples, the groups were well-matched with respect to baseline factors. The prevalences of specific aggressive behaviors on the NPI-A are summarized in Figure 2 for both the entire cohort and the moderate-severe aggression cohort. Although the frequency and severity ratings differed, the prevalences for each behavior were similar.

[Figure 1 about here]

[Table 2 about here]

[Figure 2 about here]

**Moderate or Severe Aggression Sample**

The aggression cohort group comparisons of change from baseline to Day 28 and baseline to Day 60 for the ordinal outcome measures are summarized in Table 3. For illustrative purposes, the mean NPI-A Most Problematic scores at each assessment period for Participants and Observers are depicted in Figure 3.

*Day 28:* Group comparison of change in the measures from baseline to Day 28 were not significant on the NPI-A or STAXI-2 Observer or Participate rated ordinal measures nor were the percentage who improved at least 3 points on Observer NPI-A [58.3% in amantadine vs. 53.7% in placebo (p=0.6189)] or at least 3 points on Participant NPI-A Most Problematic [40.0% in amantadine vs. 41.8% in placebo (p=0.8429)].

*Day 60:* Change in Participant-rated NPI-A Most Problematic was statistically significant (adjusted p=0.0118) in favor of amantadine. Similarly, change in Participant Distress was significantly improved (adjusted p=0.0118) in the amantadine group compared to placebo group for those with baseline Observer Distress score >2. There were no group differences on the NPI-A Observer or Observer or Participant STAXI-2 ordinal outcomes. There were no significant differences for the percentage who improved at least 3 points on Observer NPI-A [70.2% in amantadine vs. 55.6% in placebo (p=0.1107); (i.e.: 15% more people in the amantadine group were responders)] or at least 3 points on Participant NPI-A Most Problematic [47.4% in amantadine vs. 38.2% in placebo (p=0.3260); (i.e.: 7% more people in the amantadine group were responders)].

[Table 3 about here]

[Figure 3 about here]

### Entire Sample

On baseline Observer ratings, 29.2% had mild aggression (NPI-A score of 1-5) and 0.6% had no aggression; participant baseline ratings included 44.1% with mild aggression and 7.7% with no aggression. Baseline observer distress was 0 for 1.2% and 1-2 for 9.5%; baseline participant distress was 0 in 15.5% and 1-2 in 25.6% cases. The group comparisons for change from baseline to Day 28 and baseline to Day 60 for the ordinal outcome measures are summarized in supplemental digital content Table 4 and Figure 4.

### Adverse Events

Amantadine was well tolerated among study participants with no significant between groups differences on withdrawals/lost or adverse events (using Fisher's Exact Test). Adverse events are summarized elsewhere.[9]

## DISCUSSION

This is the largest study of aggression and anger treatment among those with chronic TBI (> 6 months post-injury). While both amantadine and placebo groups showed improvement on the measures, several analyses of Participant ratings demonstrated superior improvements in the magnitude and frequency of change in aggression for the amantadine group, while the changes in anger ratings were not superior. Taken together these findings suggest that the hypothesis that amantadine may be an effective intervention for reducing post-TBI aggression frequency severity and distress (Day-60

NPI-A Most Problematic and NPI-A Distress) from the perspective of the person with brain injury is accepted, but not from the observer perspective. The hypothesis that anger is reduced by amantadine is not accepted.

As was seen in the earlier (primary) study of the effect of amantadine on post-TBI irritability, (Hammond et al., 2015) substantial improvement was seen for participants in the control condition for virtually all outcome measures. The occurrence of such frequent improvement in the control group may have complicated our ability to detect a treatment effect for amantadine. In the earlier report of analyses of irritability data,[9] we discussed possible factors that may have been contributed to this placebo effect in greater detail, including behavioral monitoring[19] and nonspecific factors, such as, therapeutic alliance and positive expectations.[20,21] Study participants were required to have significant irritability but not aggression. Consequently, it seems unlikely that regression to the mean can explain the positive effect on aggression for the control group. Since all participants were more than 6 months post-injury, spontaneous recovery also seems unlikely as a cause of the improvement for controls. Clinical trial designs such as a Sequential Parallel Comparison Design and placebo run-in will need to be considered given the large placebo response in the control group.[22] The role of the placebo especially when manipulating dopaminergic therapy and seeking a chronic behavioral target will also need to be considered.[23]

The findings may have revealed clinical significance without reaching statistical significance. The comparisons of the "proportion of clinically meaningful NPI-A responders" all favored amantadine over placebo with up to 10-15% more responders. Although many of these comparisons did not reach statistical significance, it is worth

considering if this might have clinical significance. Although the outcome measures were chosen for their prior use and sensitivity in brain injury and dementia populations, it is possible that the measures lack the sensitivity needed to detect and differentiate meaningful changes for this intervention.

There are several potential reasons why between group difference in participant ratings were significant while observer ratings were not. It is worth noting that the participant NPI-A ratings at baseline were lower than the observer ratings for both the entire sample and the aggressive subset, as depicted in Figure 1 and 2. This may be, in part, due to impaired self-awareness and participant awareness of moderate-severe aggression not needed for study inclusion. Having rated themselves lower at baseline, this would be expected to impact the proportion who could possibly improve by at least three points. That is, many participants may have started at a level that left little or no room to reach our predefined level of clinically meaningful difference. The amount and nature of burden would have varied across observers. Additionally, observer burden may take longer observation period or more change to differentiate treatment from placebo on observer ratings.

The evidence base for pharmacologic treatment of aggression for those with post-acute TBI remains limited. The current findings make a contribution to this evidence by providing modest, but encouraging evidence that amantadine may provide some benefit in treating aggression persons with TBI. As reported by Hammond et al. (2015), the side effect profile of amantadine in this trial was favorable with no consequential difference in side effects between the amantadine and placebo groups. However, prescribers should be aware that individuals with uncontrolled seizure disorder, psychosis, and renal

impairment were not included in this study, and amantadine, at least at the tested dosing, should not be used in the presence of renal failure.[24] Given the favorable safety findings and modest evidence of reduction of aggressive, clinicians can consider amantadine as a possible treatment for post-TBI aggression. However, given limited evidence to this point, treated patients should be followed closely to ensure that any response to intervention is favorable.

A few limitations should be considered. First, subjective measures were used in order to capture anger and aggression during daily living given the impracticality of outcome examiners directly observing behavioral episodes in which aggression might occur in an outpatient setting over a prolonged time period. Second, the observers were not required to have a caregiving role with the participant or bear the brunt of the participant's behaviors. Third, no particular level of observer or participant distress was required for enrollment. Fourth, this study may not have been adequately powered to detect a possible beneficial impact of anger. Lastly, the study centered on *chronic* aggression and may not generalize to aggressive behaviors or anger during the acute period after TBI.

## CONCLUSION

Amantadine 100 mg twice daily in this population with chronic TBI (> 6 months post-injury) appears to be beneficial in decreasing aggression, particularly from the perspective of the individual with brain injury. Further studies may be needed to detect

effect of amantadine on anger using larger sample size, different measures, and study design that better accounts for placebo effects.

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**Figure 1: CONSORT diagram showing study flow**

**Figure 2: Prevalences of Baseline Aggressive Behaviors**

**Figure 3: Mean Observer and Participant ratings for NPI – Aggression Most Problematic at Baseline, Day 28, and Day 60 for the Moderate-Severe Aggression Subset**

**Figure 4 Supplemental Digital Content: Mean Observer and Participant ratings for NPI – Aggression Most Problematic at Baseline, Day 28, and Day 60 for the Entire Sample**

**Table 1: Eligibility Criteria**

| **INCLUSION CRITERIA:** |
|---|
| Moderate, severe, or complicated mild traumatic closed head injury (defined as impaired brain function resulting from externally inflicted trauma without penetrating injury) at least 6 months prior to enrollment with evidence from medical record, clinician report, and/or detailed history to meet one of the following criteria:<br>-post-resuscitation Glasgow Coma Scale (GCS) score 13 or lower;<br>-if patient intubated and off paralytics, post-resuscitation GCS Motor < 6;<br>-loss of consciousness attributable to the brain injury;<br>-disorientation attributable to the brain injury and persisting ≥ 24 hours;<br>-post-traumatic amnesia lasting ≥ 24 hours;<br>-neuro-imaging study with TBI-related findings such as contusion, hematoma, hemorrhage, diffuse axonal injury, shear injury, and/ or depressed skull fracture;<br>-other evidence of TBI-related focal neurological findings<br>Intoxication, sedation, intubation, or paralytics not cause of impaired consciousness. |
| Irritability that is either new or worse than level of irritability before the TBI |
| Age at time of enrollment: 16 to 75 years |
| Voluntary informed consent and authorization of participant and observer |
| Subject and observer willing to comply with the protocol |
| Observer-rated NPI Irritability Domain score 6 or greater (moderate-to-severe irritability) |
| Medically and neurologically stable during the month prior to enrollment |
| No change in medications planned during study or during month prior to enrollment |
| No surgeries planned during study |
| Any rehabilitation, psychological, and behavioral therapies commenced at least one month prior to enrollment and none planned to start during study |
| Vision, hearing, speech, motor function, and comprehension sufficient to complete interviews |
| Observer (e.g.: family member, close friend, employer) with whom subject interacts sufficiently to observe occurrences of irritability. |
| **EXCLUSION CRITERIA:** |
| Previous participation in the single-site amantadine irritability study |
| Ingestion of amantadine hydrochloride during the month prior to enrollment |
| Potential subject without a reliable observer |
| Penetrating head injury as defined by head injury due to gunshot, projectile or foreign object |
| Injury < 6 months prior to enrollment |
| Inability to interact sufficiently for communication |
| Clinical signs of active infection |
| Diagnosis of seizure in the month prior to enrollment |
| Creatinine clearance <60 mL/min (calculated using serum creatinine) |
| Pregnancy, lactating female; sexually active female without use of birth control |
| Concurrent use of neuroleptic agents |
| Concurrent active enrollment and participation in a different treatment study |
| History of schizophrenia or psychosis |
| Active concern of potential harm to self or others |
| Diagnosis of progressive or additional neurologic disease that affects brain function |
| Previous allergy or adverse reaction to amantadine hydrochloride |

**Table 2: Baseline Participant Characteristics by Treatment Group for Entire Sample and Subset with Moderate or Severe Aggression:**

| Variable | Category | Placebo (n=86) | Amantadine (n=82) | p-value | Placebo (n=57) | Amantadine (n=61) | p-value |
|---|---|---|---|---|---|---|---|
| | | % | % | | % | % | |
| | | **Entire Sample** | | | **Moderate or Severe Aggression (NPI-A ≥6)** | | |
| Gender | Male | 74.4% | 80.5% | 0.3473 | 75.4% | 83.6% | 0.2707 |
| Race | Caucasian | 87.2% | 89.0% | 0.9359 | 84.2% | 90.2% | 0.6478 |
| | Black | 5.8% | 6.1% | | 8.8% | 4.9% | |
| | Other | 7.0% | 4.9% | | 7.0% | 4.9% | |
| Hispanic | Yes | 9.3% | 3.7% | 0.1394 | 8.8% | 4.9% | 0.4802 |
| Education | Less than HS | 16.3% | 6.1% | 0.3472 | 19.3% | 3.3% | 0.1805 |
| | HS diploma | 30.2% | 37.8% | | 29.8% | 42.6% | |
| | Some college | 34.9% | 34.1% | | 38.6% | 34.4% | |
| | Bachelors or toward masters | 11.6% | 14.6% | | 7.0% | 13.1% | |
| | Masters and above | 7.0% | 7.3% | | 5.3% | 6.6% | |
| Cause of injury | Vehicular | 61.6% | 69.5% | 0.5513 | 57.9% | 73.8% | 0.2069 |
| | Fall | 18.6% | 13.4% | | 17.5% | 11.5% | |
| | Assault | 10.5% | 6.1% | | 14.0% | 6.6% | |
| | Sport-related | 3.5% | 1.2% | | 5.3% | 0% | |
| | Pedestrian | 3.5% | 7.3% | | 3.5% | 4.9% | |
| | Other | 2.3% | 2.4% | | 1.8% | 3.3% | |
| Loss of consciousness duration | <1 hour | 27.9% | 23.1% | 0.6845 | 33.3% | 20.3% | 0.2867 |
| | ≥1 hour but <24 hours | 15.1% | 12.8% | | 15.8% | 15.3% | |
| | 1-6 days | 16.3% | 24.4% | | 15.8% | 27.1% | |
| | 7-13 days | 8.1% | 6.4% | | 7.0% | 8.5% | |
| | 14-20 days | 9.3% | 12.8% | | 8.8% | 10.2% | |
| | 21-29 days | 10.5% | 9.0% | | 7.0% | 6.8% | |
| | 30-59 days | 9.3% | 6.4% | | 10.5% | 8.5% | |
| | ≥60 days | 3.5% | 5.1% | | 1.8% | 3.4% | |
| | <24 hours | 9.6% | 11.5% | 0.9685 | 10.9% | 10.3% | 0.3444 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Post-traumatic amnesia duration | 1-6 days | 22.9% | 11.5% | | 27.3% | 12.1% | |
| | 7-13 days | 4.8% | 10.3% | | 5.5% | 10.3% | |
| | 14-20 days | 9.6% | 14.1% | | 10.9% | 17.2% | |
| | 21-29 days | 12.0% | 10.3% | | 14.5% | 10.3% | |
| | 30-59 days | 15.7% | 23.1% | | 10.9% | 20.7% | |
| | ≥60 days | 25.3% | 19.2% | | 20.0% | 19.0% | |
| History >1 TBI | Yes | 18.6% | 13.4% | 0.3599 | 24.6% | 11.5% | 0.0633 |
| Total Glasgow Coma Scale score | 3-8 | 30.8% | 22.5% | 0.4672 | 30.8% | 18.5% | 0.2109 |
| | 9-12 | 1.3% | 4.2% | | 0% | 1.9% | |
| | 13-15 | 25.6% | 23.9% | | 28.8% | 24.1% | |
| | Chemically paralyzed, chemically induced coma, or intubated | 42.3% | 49.3% | | 40.4% | 55.6% | |
| | | Median ($Q_1$, $Q_3$) | Median ( $Q_1$, $Q_3$) | | Median ( $Q_1$, $Q_3$) | Median ( $Q_1$, $Q_3$) | |
| Age at enrollment | | 38.1 (26.2, 47.2) | 38.6 (30.7, 52.2) | 0.2814 | 35.5 (26.2, 46.0) | 37.6 (30.9, 50.4) | 0.3830 |
| Age at injury | | 30.5 (22.0, 40.9) | 32.3 (22.8, 42.2) | 0.3803 | 28.3 (21.4, 40.5) | 30.0 (23.9, 39.6) | 0.3771 |
| Observer NPI irritability Most Problematic | | 8.0 (6.0, 9.0) | 8.0 (6.0, 12.0) | 0.7859 | 9.0 (8.0, 9.0) | 9.0 (8.0, 12.0) | 0.3609 |
| Participant NPI irritability Most Problematic | | 6.0 (3.0, 8.0) | 6.0 (3.0, 8.0) | 0.8593 | 6.0 (4.0, 8.0) | 6.0 (4.0, 9.0) | 0.9016 |
| Observer NPI irritability Most Problematic Distress | | 4.0 (3.0, 4.0) | 4.0 (3.0, 4.0) | 0.5421 | 4.0 (3.0, 5.0) | 4.0 (3.0, 5.0) | 0.6936 |
| Participant NPI irritability Most Problematic Distress | | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) | 0.9427 | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) | 0.5415 |
| Observer NPI aggression Most Problematic | | 6.0 (4.0, 8.0) | 6.0 (4.0, 8.0) | 0.7593 | 8.0 (6.0, 9.0) | 8.0 (6.0, 9.0) | 0.5715 |
| Participant NPI aggression Most Problematic | | 4.0 (2.0, 8.0) | 6.0 (2.0, 8.0) | 0.5606 | 6.0 (3.0, 8.0) | 6.0 (3.0, 8.0) | 0.8491 |
| Observer NPI aggression Most Problematic Distress | | 4.0 (3.0, 5.0) | 4.0 (3.0, 4.0) | 0.4941 | 4.0 (3.0, 5.0) | 4.0 (3.0, 4.0) | 0.0796 |
| Participant NPI aggression Most Problematic Distress | | 3.0 (1.0, 4.0) | 3.0 (1.0, 4.0) | 0.5232 | 3.0 (2.0, 4.0) | 3.0 (1.0, 4.0) | 0.2289 |
| Beck′s Depression Inventory-II Total | | 18.5 (11.0, 30.0) | 19.0 (10.0, 28.0) | 0.6613 | 19.0 (12.0, 30.0) | 18.0 (9.0, 27.0) | 0.2489 |
| Glasgow Coma Scale-Extended | | 5.0 (4.0, 6.0) | 5.0 (5.0, 6.0) | **0.0492*** | 5.0 (4.0, 6.0) | 6.0 (5.0, 6.0) | 0.0745 |

*=*statistically significant*
$Q_1$ = 25$^{th}$ percentile, $Q_3$ = 75th percentile

**Table 3: Group Comparison of Change in Observer and Participant Ratings of Aggression and Anger from Baseline to Days 28 and 60 for *Subset with Moderate or Severe Aggression (NPI-A ≥6)*: Amantadine N = 61) versus Placebo (N = 57)**

| Variable | Group | Mean Change (SD) | Median Change ($Q_1$, $Q_3$) | p-value | Adjusted p-value |
|---|---|---|---|---|---|
| **Baseline to Day 28** | | | | | |
| NPI-A Most Problematic Observer | Placebo | -2.70 (3.42) | -3.0 (-5.0, 0.0) | 0.3618 | 0.7236 |
| | Amantadine | -3.33 (3.13) | -3.0 (-6.0, 0.0) | | |
| NPI-A Most Problematic Participant | Placebo | -3.38 (3.61) | -5.0 (-6.0, 0.0) | 0.4741 | 0.4741 |
| | Amantadine | -4.15 (3.38) | -4.0 (-6.0, -2.0) | | |
| NPI-A Distress Observer for those with distress >2 | Placebo | -1.15 (1.66) | -1.0 (-2.0, 0.0) | 0.9374 | 0.9374 |
| | Amantadine | -1.09 (1.28) | -1.0 (-2.0, 0.0) | | |
| NPI-A Distress Participant for those with distress >2 | Placebo | -1.18 (1.57) | -1.0 (-3.0, 0.0) | 0.1111 | 0.2222 |
| | Amantadine | -1.97 (1.97) | -2.0 (-4.0, 0.0) | | |
| STAXI State Anger Observer | Placebo | -2.88 (11.74) | 0.0 (-9.0, 3.0) | 0.5937 | 1.0000 |
| | Amantadine | -2.73 (12.56) | -1.0 (-9.0, 0.0) | | |
| STAXI State Anger Participant | Placebo | -2.86 (5.99) | 0.0 (-4.0, 0.0) | 0.3102 | 0.8080 |
| | Amantadine | -1.95 (7.91) | 0.0 (-4.0, 0.0) | | |
| STAXI Trait Anger Observer | Placebo | -9.62 (13.12) | -7.0 (-17.0, 0.0) | 0.5604 | 1.0000 |
| | Amantadine | -8.10 (13.06) | -8.0 (-18.0, 0.0) | | |
| STAXI Trait Anger Participant | Placebo | -9.08 (12.41) | -8.0 (-14.0, 0.0) | 0.3940 | 0.8080 |
| | Amantadine | -11.51 (12.36) | -10.0 (-18.0, -2.0) | | |
| STAXI Anger Expression Observer | Placebo | -6.73 (11.20) | -4.0 (-11.0, 0.0) | 0.1546 | 0.4638 |
| | Amantadine | -8.07 (9.48) | -6.0 (-15.0, -2.0) | | |
| STAXI Anger Expression Participant | Placebo | -5.78 (9.53) | -4.0 (-12.0, 0.0) | 0.2693 | 0.8080 |
| | Amantadine | -9.76 (14.08) | -8.0 (-20.0, 0.0) | | |
| **Baseline to Day 60** | | | | | |
| NPI-A Most Problematic Observer | Placebo | -3.04 (4.09) | -3.5 (-6.0, 0.0) | 0.2062 | 0.4123 |
| | Amantadine | -3.91 (3.15) | -4.0 (-6.0, -2.0) | | |
| NPI-A Most Problematic Participant | Placebo | -2.89 (3.31) | -3.0 (-6.0, 0.0) | **0.0059*** | **0.0118*** |
| | Amantadine | -5.27 (3.52) | -6.0 (-8.0, -2.0) | | |
| NPI-A Distress Observer for those with distress >2 | Placebo | -1.26 (1.68) | -1.0 (-2.0, 0.0) | 0.2623 | 0.4123 |
| | Amantadine | -1.54 (1.34) | -2.0 (-2.0, -1.0) | | |
| NPI-A Distress Participant for those with distress >2 | Placebo | -1.44 (1.52) | -1.0 (-3.0, 0.0) | **0.0086*** | **0.0118*** |
| | Amantadine | -2.56 (1.55) | -3.0 (-4.0, -1.0) | | |
| STAXI State Anger Observer | Placebo | -0.68 (14.07) | 0.0 (-4.0, 4.0) | 0.0551 | 0.1653 |
| | Amantadine | -4.95 (11.23) | -2.0 (-10.0, 0.0) | | |
| STAXI State Anger Participant | Placebo | -2.59 (9.11) | 0.0 (-6.0, 0.0) | 0.7664 | 1.0000 |
| | Amantadine | -3.24 (6.19) | -2.0 (-6.0, 0.0) | | |
| STAXI Trait Anger Observer | Placebo | -10.53 (15.05) | -6.0 (-22.0, 0.0) | 0.2574 | 0.5148 |
| | Amantadine | -12.91 (13.14) | -14.0 (-22.0, -2.0) | | |
| STAXI Trait Anger Participant | Placebo | -11.68 (10.32) | -12.0 (-18.0, -6.0) | 0.6107 | 1.0000 |
| | Amantadine | -14.16 (12.31) | -12.0 (-22.0, -4.0) | | |
| STAXI Anger Expression Observer | Placebo | -10.08 (13.13) | -8.0 (-18.0, 0.0) | 0.3311 | 0.5148 |
| | Amantadine | -10.88 (10.89) | -8.0 (-18.0, -2.0) | | |
| STAXI Anger Expression Participant | Placebo | -6.92 (9.84) | -6.0 (-12.0, 0.0) | **0.0195*** | 0.0586 |
| | Amantadine | -13.62 (12.96) | -12.0 (-24.0, -2.0) | | |

*= *statistically significant*

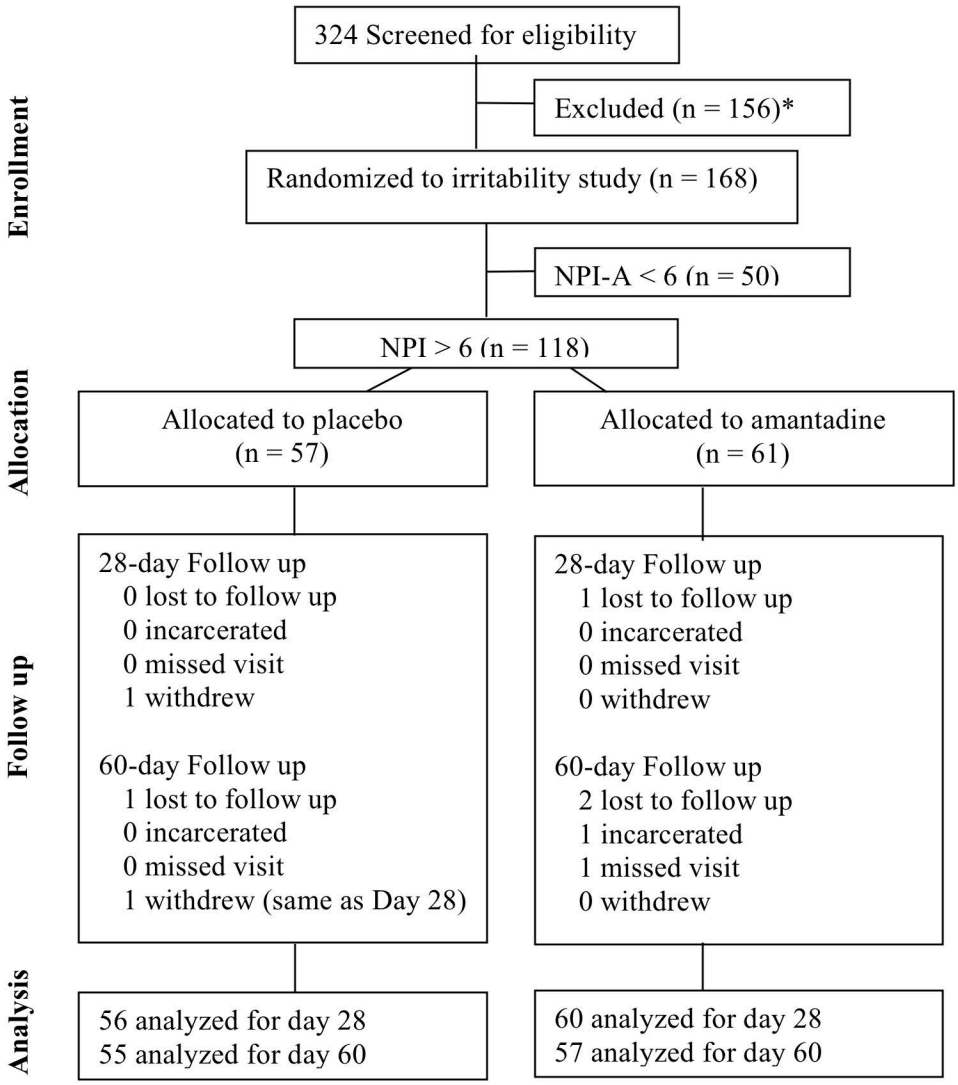
$Q_1$ = 25th percentile, $Q_3$ = 75th percentile

**Table 4 Supplemental Digital Content: Group Comparison of Change in Observer and Participant Ratings of Aggression and Anger from Baseline to Days 28 and 60 for *Entire Sample*: Amantadine N = 82) versus Placebo (N = 86)**

| Variable | Group | Mean Change (SD) | Median Change ($Q_1$, $Q_3$) | p-value | Adjusted p-value |
|---|---|---|---|---|---|
| **Baseline to Day 28** | | | | | |
| NPI-A Most Problematic Observer | Placebo | -1.28 (3.73) | -1.0 (-4.0, 2.0) | **0.0467*** | 0.0934 |
| | Amantadine | -2.38 (3.51) | -2.0 (-5.0, 0.0) | | |
| NPI-A Most Problematic Participant | Placebo | -1.57 (3.33) | -1.0 (-4.0, 0.0) | 0.2234 | 0.4467 |
| | Amantadine | -2.26 (3.44) | -2.0 (-4.0, 0.0) | | |
| NPI-A Distress Observer for those with distress >2 | Placebo | -0.96 (1.60) | -1.0 (-2.0, 0.0) | 0.1800 | 0.1800 |
| | Amantadine | -1.24 (1.36) | -1.0 (-2.0, 0.0) | | |
| NPI-A Distress Participant for those with distress >2 | Placebo | -1.38 (1.75) | -1.0 (-3.0, 0.0) | 0.2321 | 0.4467 |
| | Amantadine | -1.86 (1.86) | -1.5 (-3.0, 0.0) | | |
| STAXI State Anger Observer | Placebo | -2.28 (11.86) | 0.0 (-8.0, 2.0) | 0.9624 | 1.0000 |
| | Amantadine | -1.18 (12.94) | 0.0 (-8.0, 2.0) | | |
| STAXI State Anger Participant | Placebo | -1.98 (8.80) | 0.0 (-4.0, 0.0) | 0.1898 | 0.2784 |
| | Amantadine | -1.09 (7.01) | 0.0 (-4.0, 0.0) | | |
| STAXI Trait Anger Observer | Placebo | -8.15 (13.31) | -6.0 (-16.0, 0.0) | 0.3561 | 1.0000 |
| | Amantadine | -6.60 (12.85) | -3.0 (-15.0, 0.0) | | |
| STAXI Trait Anger Participant | Placebo | -7.01 (10.92) | -4.0 (-12.0, 0.0) | 0.1025 | 0.2784 |
| | Amantadine | -10.05 (11.48) | -8.0 (-16.0, 0.0) | | |
| STAXI Anger Expression Observer | Placebo | -6.68 (11.81) | -4.0 (-12.0, 2.0) | 0.4628 | 1.0000 |
| | Amantadine | -6.78 (10.71) | -6.0 (-13.0, 0.0) | | |
| STAXI Anger Expression Participant | Placebo | -4.59 (9.00) | -4.0 (-10.0, 2.0) | 0.0928 | 0.2784 |
| | Amantadine | -7.82 (11.61) | -4.0 (-16.0, 0.0) | | |
| **Baseline to Day 60** | | | | | |
| NPI-A Most Problematic Observer | Placebo | -1.61 (4.31) | -2.0 (-4.0, 0.0) | **0.0245*** | **0.0491*** |
| | Amantadine | -3.01 (3.41) | -3.0 (-5.0, 0.0) | | |
| NPI-A Most Problematic Participant | Placebo | -1.61 (2.82) | -1.0 (-3.0, 0.0) | 0.1592 | 0.1592 |
| | Amantadine | -2.63 (3.95) | -2.0 (-6.0, 0.0) | | |
| NPI-A Distress Observer for those with distress >2 | Placebo | -1.19 (1.66) | -1.0 (-2.0, 0.0) | 0.0601 | 0.0601 |
| | Amantadine | -1.66 (1.36) | -2.0 (-3.0, -1.0) | | |
| NPI-A Distress Participant for those with distress >2 | Placebo | -1.60 (1.75) | -1.0 (-3.0, 0.0) | 0.0659 | 0.1318 |
| | Amantadine | -2.25 (1.53) | -2.0 (-3.0, -1.0) | | |
| STAXI State Anger Observer | Placebo | -0.84 (12.88) | 0.0 (-4.0, 4.0) | **0.0359*** | 0.1078 |
| | Amantadine | -4.05 (12.10) | -2.0 (-10.0, 0.0) | | |
| STAXI State Anger Participant | Placebo | -1.66 (9.75) | 0.0 (-4.0, 0.0) | 0.7125 | 0.8338 |
| | Amantadine | -1.52 (7.00) | 0.0 (-4.0, 0.0) | | |
| STAXI Trait Anger Observer | Placebo | -9.73 (14.61) | -8.0 (-22.0, 0.0) | 0.3968 | 0.6920 |
| | Amantadine | -11.41 (13.37) | -12.0 (-22.0, 0.0) | | |
| STAXI Trait Anger Participant | Placebo | -8.93 (9.95) | -8.0 (-14.0, -2.0) | 0.4169 | 0.8338 |
| | Amantadine | -10.69 (12.23) | -10.0 (-20.0, -2.0) | | |
| STAXI Anger Expression Observer | Placebo | -9.69 (13.21) | -6.0 (-18.0, 0.0) | 0.3460 | 0.6920 |
| | Amantadine | -10.16 (10.95) | -8.0 (-18.0, -2.0) | | |
| STAXI Anger Expression Participant | Placebo | -6.00 (10.23) | -5.0 (-10.0, 2.0) | 0.0707 | 0.2120 |
| | Amantadine | -9.39 (11.65) | -8.0 (-16.0, 0.0) | | |

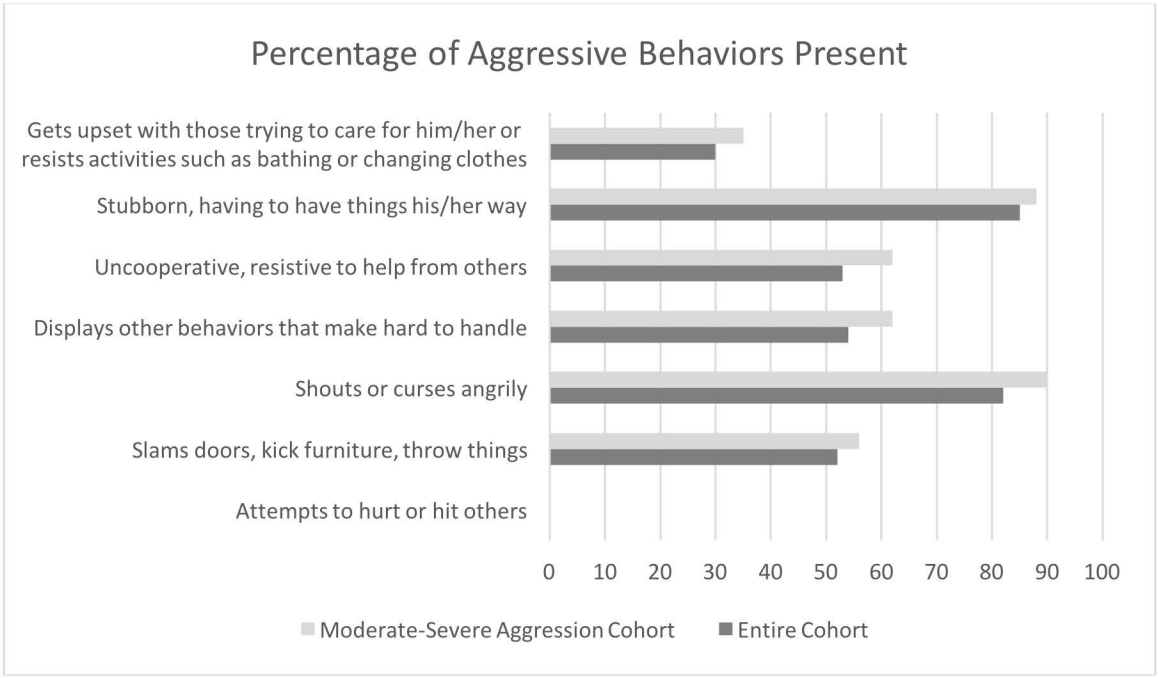
*= *statistically significant*

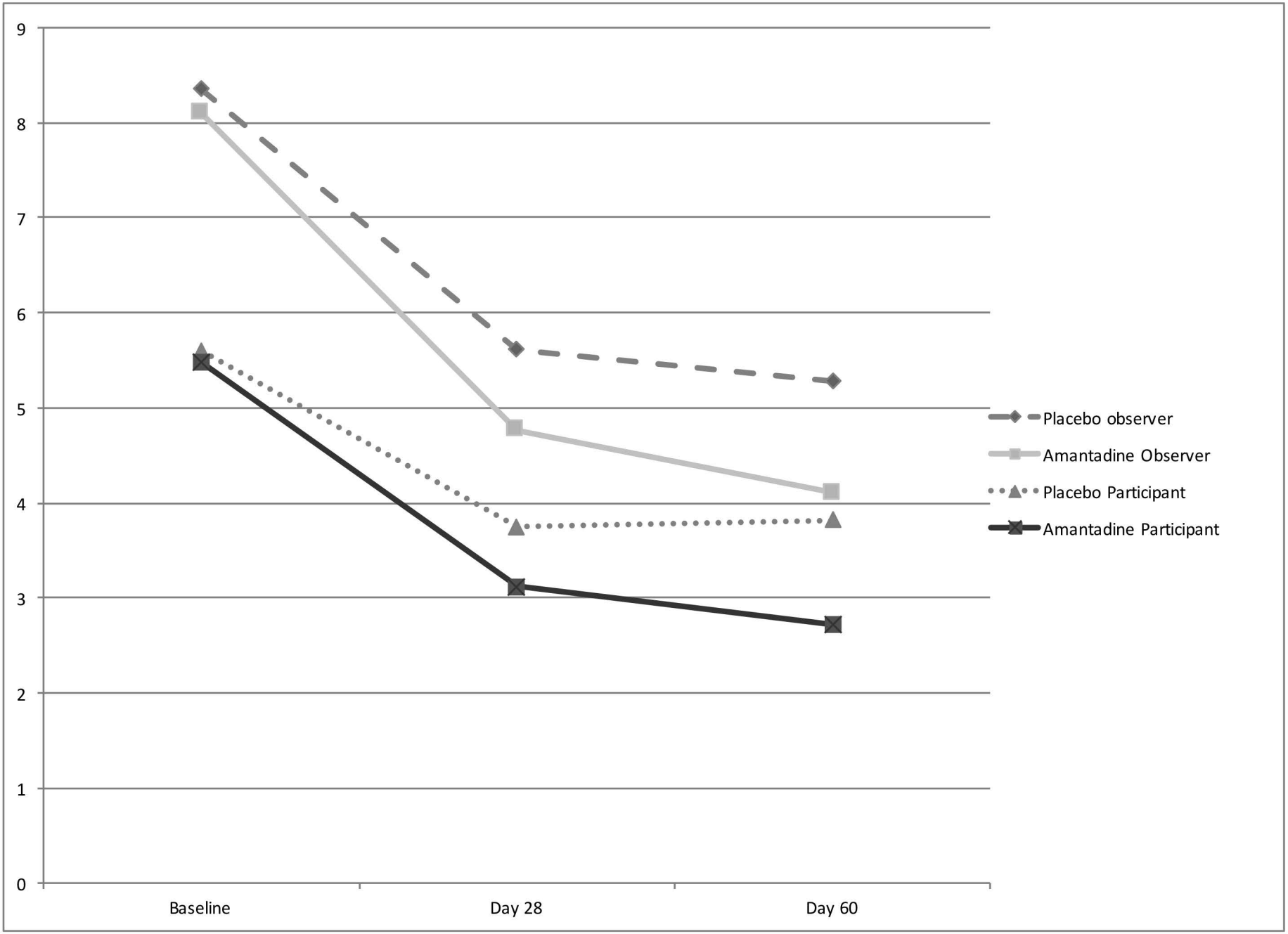
$Q_1$ = 25$^{th}$ percentile, $Q_3$ = 75th percentile

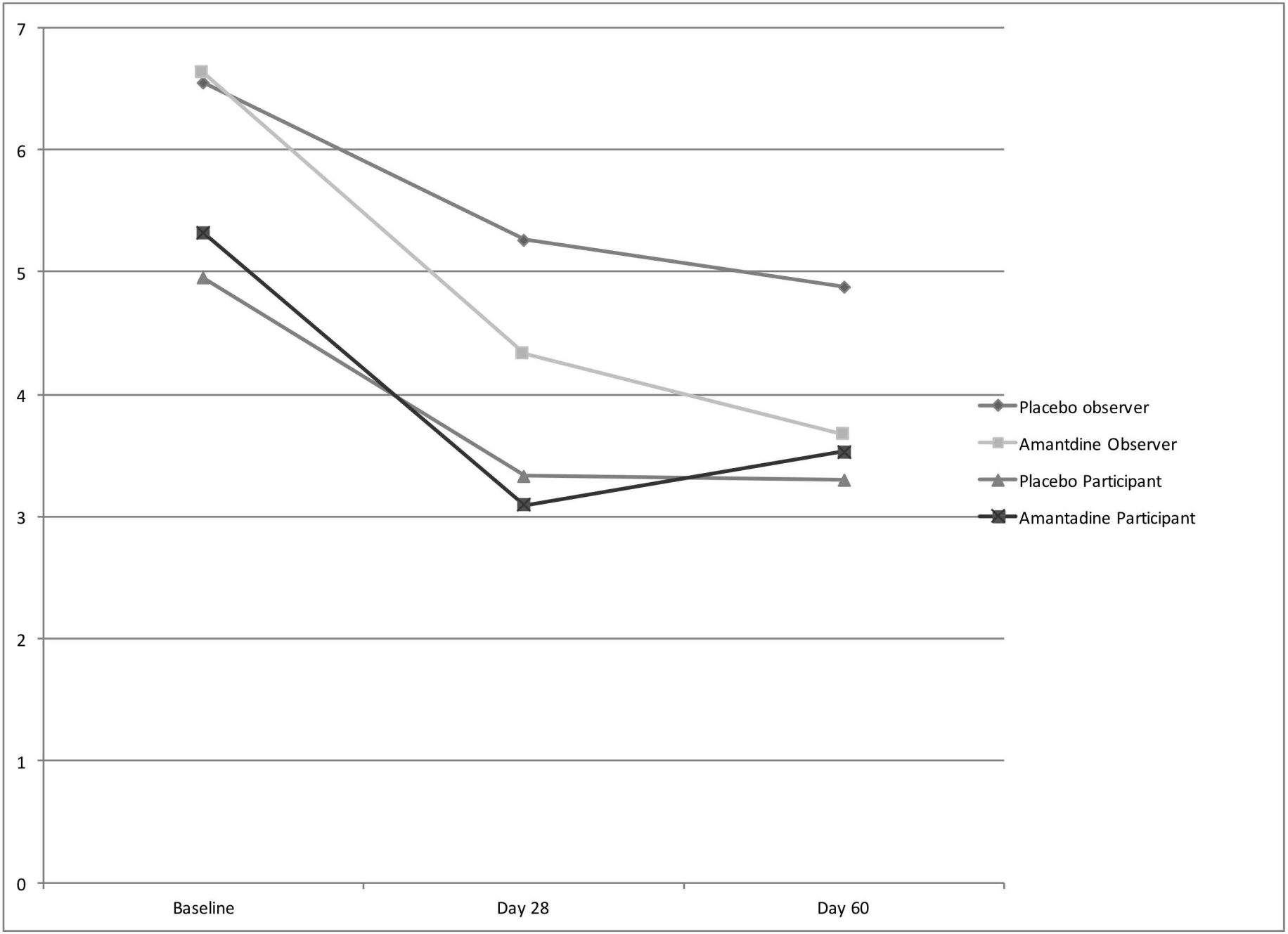



* Reasons for Exclusion (n = 156):

| | |
|---|---|
| 56 | Sustained penetrating traumatic brain injury |
| 35 | Irritability is not new or worse than before the traumatic brain injury |
| 10 | Age <16 or >75 years at time of enrollment |
| 54 | Not willing to comply with protocol |
| 70 | Observer Neuropsychiatric Inventory not greater than 6. |
| 8 | Not medically and neurologically stable |
| 2 | Taking antidepressant, anxiolytic, hypnotic, or stimulant medications with recent or expected change |
| 8 | Vision, hearing, speech, motor function, and/or comprehension not sufficient to complete interviews |
| 40 | Subject does not have observer with whom he/she interacts 5 days per week or greater |
| 4 | Previous participation in the single-site amantadine irritability study |
| 16 | Ingestion of amantadine during month prior to enrollment |
| 2 | Injury <6 months prior to enrollment |
| 4 | Seizure in the month prior to enrollment |
| 5 | Creatinine clearance <60 mL/min |
| 1 | Pregnancy-related |
| 2 | Concurrent use of first generation neuroleptic agents |
| 2 | Concurrent active enrollment in a different treatment study |
| 7 | History of schizophrenia or psychosis |
| 14 | Active concern of potential harm to self or others |
| 5 | Diagnosis of progressive or additional neurologic disease that affects brain function |
| 3 | Previous allergy or adverse reaction to amantadine |
| 23 | Other |


Percentage of Aggressive Behaviors Present
Gets upset with those trying to care for him/her or resists activities such as bathing or changing clothes
Stubborn, having to have things his/her way
Uncooperative, resistive to help from others
Displays other behaviors that make hard to handle
Shouts or curses angrily
Slams doors, kick furniture, throw things
Attempts to hurt or hit others
0 10 20 30 40 50 60 70 80 90 100
Moderate-Severe Aggression Cohort
Entire Cohort


9
8
7
6
5
4
3
2
1
0
Baseline
Day 28
Day 60
Placebo observer
Amantadine Observer
Placebo Participant
Amantadine Participant


7
6
5
4
3
2
1
0
Baseline
Day 28
Day 60
Placebo observer
Amantdine Observer
Placebo Participant
Amantadine Participant