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Efficacy of Amantadine Treatment on Symptoms and Neurocognitive Performance Among Adolescents Following Sports-Related Concussion

Cara Camiolo Reddy, MD; Michael Collins, PhD; Mark Lovell, PhD; Anthony P. Kontos, PhD

Objective: To evaluate the efficacy of amantadine in the treatment of symptoms and neurocognitive performance in adolescents following sports-related concussion. **Participants:** A clinical sample of 25 male ($n = 11$) and female ($n = 14$) adolescent subjects with an age-, sex-, and concussion history–matched group of 25 male (n = 11) and female ($n = 14$) control subjects. **Setting:** Outpatient concussion clinic. **Intervention:** Retrospective, case-control design. Treatment group consisted of patients treated with 100 mg of amantadine twice daily (200 mg total per day) following a period of rest. Matched controls were evaluated and treated conservatively without medication at the same concussion program prior to the start of the current amantadine protocol. **Main Outcome Measures:** Immediate Postconcussion Assessment and Cognitive Test computerized neurocognitive test battery and symptom report. **Results:** Results support significantly greater improvements from pre- to posttest in reported symptoms, verbal memory, and reaction time performance for the amantadine group than the matched controls. There were no significant differences for visual memory or visual motor processing speed. **Conclusion:** This study provides empirical support for amantadine as an effective pharmacologic treatment of certain concussion-related cognitive deficits and symptoms in athletes with protracted recovery of more than 3 weeks. **Key words:** *amantadine*, *concussion*, *postconcussion symptoms*

THE pathophysiology of traumatic brain injury (TBI) has been postulated to involve complex biochemical cascades leading to dysregulation of ions and neurotransmitters, as well as increases in inflammatory mediators and free radical production.[1] Disruption in the release and uptake of neurotransmitters has been considered a likely source of the neurocognitive sequelae of TBI. For individuals who have sustained a mild TBI, or concussion, these disruptions clinically manifest in an array of symptoms including physical, cognitive, emotional, or sleep-related disturbances.[2]

Dopamine, in particular, is known to have strong influences in the frontal lobe and is involved in regulation of behavior, executive function, judgment, arousal, and motor control.[3] Medications that antagonize dopaminergic pathways (eg, haloperidol, risperidone) have resulted in negative consequences for recovery from TBI.[4,5] Conversely, medications that improve dopaminergic transmission (eg, bromocriptine, methylphenidate) have led to improvements in functional outcomes in animal models.[6,7] Limited but growing evidence suggests that dopaminergic neurostimulants may facilitate recovery and quality of life for persons with brain injury; however, no studies to date have addressed the effects of neurostimulants on athletes following concussion.

Amantadine is a dopaminergic agent that presynaptically facilitates the release of dopamine and inhibits reuptake, thereby increasing the concentration of dopamine in the synaptic cleft. Amantadine also has a direct postsynaptic effect on dopamine receptors that increases density and/or alters their configuration. In addition, amantadine is a noncompetitive

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N-methyl-D-aspartate antagonist that may afford neuroprotective effects through inhibition at excitatory glutamate receptors.[3]

For several decades, amantadine has been used as an antiviral agent and was subsequently found to be effective in the treatment of Parkinson disease.[8] Preliminary research and anecdotal evidence regarding the use of amantadine for the treatment of neurocognitive deficits resulting from TBI has been promising, and, as such, amantadine is often used off label for persons with mild, moderate, and severe TBI. Recognized as a safe and well-tolerated medication, the potential adverse effects of amantadine include gastrointestinal upset, insomnia, vivid dreams, anorexia, irritability, agitation, livedo reticularis, and peripheral edema. These adverse effects are dose dependent and reversible. Reported administration of amantadine for the treatment of TBI has ranged from 50 to 400 mg daily in divided doses, with a favorable onset of action of approximately 48 to 72 hours.[9] In several case studies and retrospective reviews, researchers have reported that amantadine improved cognitive function including attention, concentration, processing time, psychomotor speed, sequencing, agitation, impulsivity, perseveration, vocalizations, fatigue, initiation, participation in therapy, and response to commands and sensory stimulation.[10–17] One small placebo-controlled double-blind crossover study reported no statistical effect of amantadine on cognitive function in persons with TBI.[18] In contrast, another study using a similar design and sample reported consistent trends toward more rapid functional improvement after amantadine administration as measured by the Disability Rating Scale, Glasgow Outcome Scale, and Functional Independence Measure.[17]

To date, there have been no published empirical reports on the use of amantadine in the treatment of symptoms and cognitive deficits in athletes following concussion. Moreover, in previous literature on the use of amantadine in TBI, most participants were adults, with varying time periods between injury and therapeutic intervention and heterogeneity in mechanism and severity of injury. Therefore, the purpose of the current study was to examine changes in symptoms and neurocognitive performance from pre- to posttreatment in a sample of adolescent athletes following concussion. The treatment group received 100 mg of amantadine twice daily (200 mg per day) and was compared with a group of untreated, age-, sex-, and concussion history–matched controls. Given the reported neurocognitive benefits of amantadine for patients with TBI, the researchers hypothesized that amantadine would be efficacious in the treatment of postconcussive symptoms and cognitive deficits in individuals who have not spontaneously recovered within 3 weeks from injury. Specifically, the researchers hypothesized that the amantadine treatment group would (1) report a significantly greater decrease in symptoms from pre- to posttest and (2) score significantly better on neurocognitive tests from pre- to posttest than age-, sex-, and concussion history–matched controls. The researchers expected that participants in the control group would also improve over time, although not as much as those in the treatment group.

METHODS

Design

The retrospective case-control, pre-/posttest design used in this study was approved by the institutional review board of the University of Pittsburgh.

Participants

A clinical sample of 25 adolescents (11 male, 14 female participants) evaluated and treated at the UPMC Sports Medicine Concussion Program constituted the "treatment" participants. They were given 100 mg of amantadine twice daily at breakfast and lunch (200 mg total per day) for an average of 3 to 4 weeks after failing to recover following a period of rest of approximately 21 days. An age-, sex-, and concussion history–matched group of 25 adolescents evaluated and treated conservatively (ie, rest) without medication at the same clinical concussion program prior to the start of the current amantadine protocol was selected as controls. These individuals did not receive any confounding pharmacologic treatments, and all nonpharmacologic treatment (ie, education) was consistent between groups. Inclusion criteria for all were (1) 13 to 19 years of age and (2) a diagnosis of current symptomatic sports-related concussion. Exclusion criteria were (1) history of migraines, headaches, neurologic disorder, sleep disorder, or attention-deficit disorder and/or attention-deficit/hyperactivity disorder; (2) diagnosis of major psychiatric disorder; (3) current, or history of, substance abuse; (4) contraindications for treatment with amantadine; or (5) concurrent pharmacologic treatment involving medications with known central nervous system or symptom-modifying effects. The average age was 15.54 (SD = 1.42) years. Demographic and testing information for the treatment and control groups is provided in Table 1. There were no significant group differences on any of these variables.

Outcome measures

All participants completed the Immediate Postconcussion Assessment and Cognitive Test (ImPACT) computerized neurocognitive test battery and symptom report. The ImPACT comprises a series of 6 modules that yield 4 composite scores: verbal memory (% correct), visual memory (% correct), visual processing speed

TABLE 1 *Summary of demographic and test variables for the amantadine (n = 25) treatment and matched control (n = 25) subjects and results of independent sample t tests*

	M (SD)			t test	
	Total	Amantadine group	Control group	t	P
Age, y	15.54 (1.42)	15.68 (1.44)	15.40 (1.41)	0.70	.49
Concussion history, *n*	0.68 (1.17)	0.56 (0.92)	0.80 (1.38)	−0.72	.47
Injury to pretest, d	26.18 (36.70)	26.16 (28.16)	26.24 (44.21)	−.01	.99
Injury to posttest, d	47.64 (57.10)	48.88 (41.85)	46.40 (70.00)	0.15	.88

(higher number = better performance), and reaction time (in seconds, lower number = better performance). The ImPACT also contains a 22-item self-report symptom inventory that includes items for problems such as headache, dizziness, memory problems, difficulty concentrating, anxiety, depression, and sleep. The concussion symptom inventory uses a 7-point Likert-type scale in which 0 is a complete absence of symptoms and 6 is the most severe.[19–21] The ImPACT and symptom report have been reported to be both valid and reliable in previous studies.[22–27]

Procedures

All individuals selected for the study sustained a sports-related concussion and were referred for evaluation to the UPMC Sports Medicine Concussion Program by an emergency department, high school athletic trainer, or physician. As most were injured while playing organized sports, concussions were diagnosed initially by certified athletic trainers and/or team physicians present on the sidelines. The basis for diagnosis was presentation of 1 or more of the following signs or symptoms after a direct or indirect impact to the head: (1) any noticeable change in mental status; (2) loss of consciousness, disorientation, posttraumatic amnesia, or retrograde amnesia; or (3) any self-reported symptoms (eg, headache, dizziness, balance dysfunction, visual blurring, diplopia) that appeared following a direct or indirect impact to the head. For individuals who were not injured while playing organized sports, concussions were diagnosed by emergency or family medical personnel and subsequently referred to the clinic for evaluation and treatment. All initial diagnoses were confirmed by clinical personnel (ie, neuropsychologists or physicians) using the aforementioned description.

Following injury, all participants completed a clinical neuropsychological interview that included self-report and information from their parents. At that time, they also completed the pretest ImPACT battery and symptom report (see Table 1 for average times from injury to pre- and posttests). It is standard protocol at the UPMC Sports Medicine Concussion Program to refer patients for medical evaluation and treatment when their symptoms from concussion have not abated within 21 to 30 days postinjury. Pharmacologic treatments are introduced if the athlete has not shown significant signs of recovery within this 3- to 4-week period following injury, as research from our group indicates that 80% of athletes recover spontaneously within this time.[28]

Those in the treatment group were given 100 mg of amantadine twice daily for 3 to 4 weeks. None discontinued the medication because of adverse effects. Those in the control group were not given medication, as they were admitted to the clinic prior to the implementation of the current medication protocols. Those in both groups were tested again using the ImPACT and the symptom report at approximately 40 to 50 days postinjury.

Data analysis

Repeated-measures analyses of covariance (covaried for concussion history) with Bonferroni corrections were used to compare the pre- and posttest ImPACT (ie, verbal and visual memory, visual processing speed, reaction time) and symptom scores of the amantadine treatment group with the matched controls. All statistical tests were performed using Statistical Package for the Social Sciences (SPSS: IBM) version 18. A significance level of $P < .05$ was used for all statistical tests.

RESULTS

A series of repeated-measures analyses of covariance (covaried for concussion history at a value of 0.68) supported significant within-subject effects for time across all ImPACT neurocognitive composite scores and reported symptoms (Table 2). Specifically, participants in both groups reported a decrease in symptoms and an increase in verbal and visual memory, visual processing speed, and reaction time scores from pre- to posttest. There were 3 significant between-group differences at the pretest: (1) verbal memory ($F_{1,47} = 7.90$, $P = .007$), with the amantadine group ($M = 72.52$, SD = 20.76) scoring significantly lower than the controls ($M = 84.92$, SD = 7.57); (2) visual memory ($F_{1,47} = 4.43$, $P = .04$),

TABLE 2 *Summary of within-subject effects for time (pre- to posttest) across symptoms and ImPACT composite scores (N = 50)*

	M (SD)		
	Pretest	**Posttest**	***P***
Symptoms, *n*	30.04 (20.78)	13.04 (14.10)	.001
Verbal memory, %	78.72 (16.68)	86.74 (9.59)	.001
Visual memory, %	66.00 (13.75)	77.70 (14.28)	.001
Visual processing speed, *n*	34.90 (8.71)	39.05 (8.40)	.011
Reaction time, s	0.63 (0.14)	0.56 (0.11)	.001

with the amantadine group ($M = 61.92$, SD = 16.37) scoring significantly lower than the controls ($M = 70.08$, SD = 9.14); and (3) total symptoms ($F_{1, 47} = 6.67$, $P = .01$), with the amantadine group ($M = 37.08$, SD = 20.81) scoring significantly higher than the controls ($M = 23.00$, SD = 18.60). There were no significant between-group differences at the pretest for processing speed ($P = .18$) or reaction time ($P = .13$). The time interval between pre- and posttest was 22.8 days (SD = 26.40) for the amantadine group and 20.2 days (SD = 30.91) for the control group ($t = 0.32$, $P = 0.75$).

As is evident in Table 3, 3 significant interactions between time (pre- and posttests) and group (treatment and controls) were supported for symptoms, verbal memory, and reaction time. The interaction between time and group on symptoms is represented in Figure 1. Although symptoms of both groups decreased from pre- to posttest, decrease of the treatment group was larger than that of the control group. The interaction between time and group on verbal memory is represented in Figure 2. Again, although verbal memory performance of both groups increased from pre- to posttest, increase of the treatment group was significantly larger than that of the control group. The interaction between time and group on reaction time is represented in Figure 3. Again, although reaction time performance of both groups improved (ie, decreased in time [in seconds]) from pre- to posttest, improvement of the treatment group was significantly larger than that of the control group.

DISCUSSION

Estimates indicate that several million sports- and recreation-related concussions occur annually in the United States,[29] with a majority of patients recovering spontaneously within the first 1 to 3 weeks postinjury. Unfortunately, for many individuals, symptoms including headaches, dizziness, fogginess, difficulty concentrating, sensitivity to light and noise, irritability, and sleep dysregulation persist beyond the first month after injury. These symptoms can be significantly disabling, often resulting in an inability to attend school, complete academic work, participate in sporting and extracurricular activities, and interact socially with peers.

In this study, we retrospectively evaluated a group of patients treated with amantadine alone and them compared with an age-, sex-, and concussion history–matched group of patients who went through the concussion program prior to the initiation of medication protocols. The control group did not receive any pharmacologic treatment, and neither group received any

TABLE 3 *Summary of results from the repeated-measures analyses of covariance for the amantadine (n = 25) treatment and matched control (n = 25) subjects*

	Amantadine group		**Control group**					
	Pre, *M* (SD)	**Post, *M* (SD)**	**Pre, *M* (SD)**	**Post, *M* (SD)**	**Wilk λ**	***F***	**η^2**	***P***
Symptoms, *n*	37.08 (20.81)	11.80 (11.79)	23.00 (18.59)	14.28 (16.24)	0.84	8.71	0.16	.005
Verbal memory, % correct	72.52 (20.76)	86.16 (9.13)	84.92 (7.57)	87.32 (10.18)	0.87	7.35	0.14	.009
Visual memory, % correct	61.92 (16.37)	76.68 (14.16)	70.08 (9.14)	78.72 (14.62)	0.96	2.14	0.04	0.30
Visual processing speed, *n*	33.20 (9.95)	38.20 (9.13)	36.60 (7.06)	39.91 (7.69)	0.98	0.79	0.02	0.38
Reaction time, s	0.66 (0.16)	0.56 (0.13)	0.60 (0.11)	0.56 (0.10)	0.92	3.97	0.08	0.05

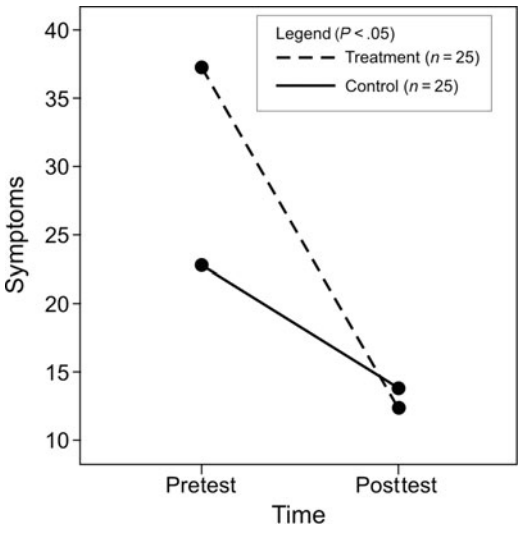

Figure 1. Symptom covariate appearing in the model is evaluated at the following value: concussion history = 0.68.

concurrent pharmacologic treatment with known central nervous system or symptom-modifying effects, including medications to treat headaches, sleep, or mood. As expected, both groups had significant within-subject improvements as noted by a decrease in reported symptoms and improvements in verbal and visual memory, visual processing speed, and reaction time from pre- to posttest. This indicates natural recovery from concussive injury, which is expected to occur over time; however, for those in the amantadine treatment group, the improvements in reported symptoms, verbal memory, and reaction time were significantly greater than those found in their matched controls, suggesting efficacy for amantadine in the treatment of these symptoms.

These results corroborate prior case reports and anecdotal evidence that amantadine positively affects cogni-

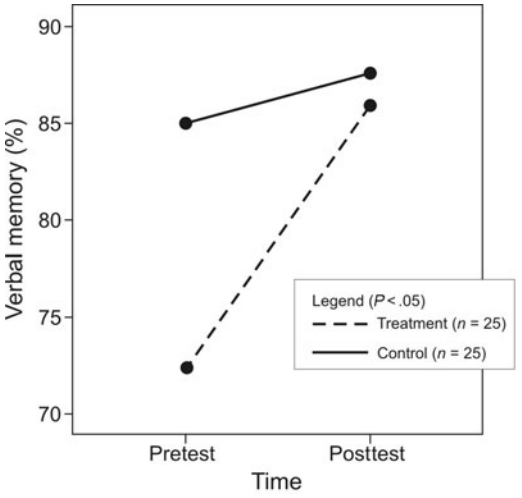

Figure 2. Verbal memory covariate appearing in the model is evaluated at the following value: concussion history = 0.68. Reproduced with permission.

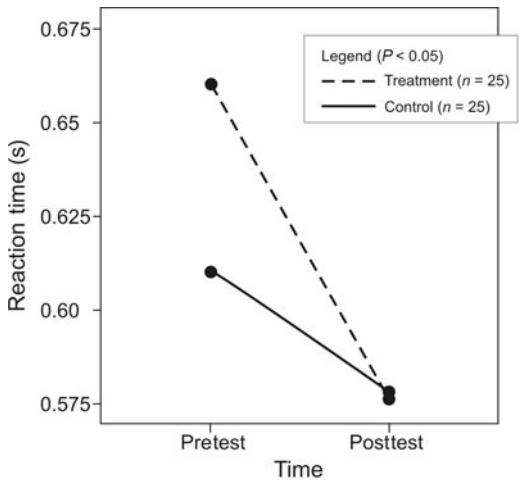

Figure 3. Reaction time covariate appearing in the model is evaluated at the following value: concussion history = 0.68.

tive processing and functional improvement when used in the treatment of TBI. This is the first study to assess the use of this medication in the treatment of student athletes following mild TBI or concussion. These results highlight one possible treatment for the patients with prolonged recovery from concussion, but the authors recognize and assert that this medication may not be the treatment of choice for all patients with postconcussive symptoms. Individualized concussion treatment requires in-depth interview to evaluate the symptoms and to tailor a management plan based upon each individual's symptom profile.

The current study was limited by several factors. Most notably, the sample size was small due to the need to limit the subject pools to patients taking amantadine only (treatment group) or no medications at all (matched controls); potential participants were excluded from both groups if they had been prescribed any other interventions such as sleep aids, pain relievers, or headache medications. Nonetheless, the small sample size could have resulted in nonrepresentative groups and spurious findings. However, the groups were matched on known factors that influence concussion outcomes including age, sex, and concussion history. Although both groups received education as part of our standard management protocols, we were unable to control for adherence to rest in the amantadine and control groups; however, there is no reason to suggest that either group would have been more or less likely to adhere appropriately. The case-control research design resulted in data that were retrospective. Premorbid differences in neurocognitive performance and symptoms could have resulted in the within-subject interaction with time reported in the present study. The nonrandomized design resulted in both participants and clinicians being aware of the use of amantadine. As such, placebo and experimenter bias (ie, the desire for amantadine efficacy) effects could

explain the results of the current study. In summary, the limitations of the current study warrant additional research using a double-blind, randomized control design involving a large sample to substantiate the findings from this initial study.

CONCLUSION

In the current study, treatment with amantadine resulted in a significant decrease in reported symptoms as well as improvements in verbal memory and reaction time performance in adolescents compared with matched controls. This finding provides tentative support for the efficacy of amantadine as pharmacologic treatment of patients who fall outside of the normal recovery trajectory (i.e., >3 weeks) following concussion. However, given the small sample size and retrospective case-control design, the results of this study should be viewed cautiously. The authors advocate for double-blind randomized control trials of the efficacy of amantadine following concussion in a sufficiently large sample to corroborate the findings of this study.

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