

## Stimulant Use to Improve Wakefulness Following Brain Injury: A Survey of the Neurocritical Care Society

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**Received:** November 20, 2019; **Published:** December 04, 2019

### Abstract

**Background:** Brain injury can have lasting neurologic sequelae. Many patients suffer from disorders of attention and arousal following severe brain injury. A majority of the therapies we offer these patients are largely supportive. Our goal was to create and distribute a clinical practice survey to evaluate which specific medications are currently being used by neurointensivists in the management of attention and arousal disorders following brain injury.

**Methods:** An 8 question unvalidated survey was organized and distributed to the 1366 members of the Neurocritical Care Society (NCS), made up of neurointensivists, medical intensivists, neurosurgeons and anesthesiologists. The survey was conducted from November 15, 2013 through November 29, 2013.

**Results:** 122 responses were obtained. More than half of respondents were neurointensivists (54.9%). 59.8% of the respondents selected amantadine as their medication of choice to address attention and arousal issues. 69.4% of the respondents initiated therapy more than a week out from injury. 34.4% of the respondents treat their patients for more than 2 weeks. 55.7% of respondents reported trying another agent, if the initial selection did not improve wakefulness. 76.2% selected traumatic brain injury (TBI) as the primary diagnosis of patients receiving pharmacologic treatment. Overall, 50.4% of the respondents felt that medications were effective only a quarter of the time. Only a single respondent reported an institutional protocol for administering stimulants for wakefulness.

**Conclusion:** Amantadine is used most frequently; however, the medications and time schedules that are utilized vary. Only one respondent reported an institutional policy that directs therapy.

**Keywords:** Amantadine; Stimulants; Brain Injury; Disorders of Attention and Arousal

### Introduction

Trauma is the leading cause of death for Americans under the age 44. In the United States, 30% of these deaths are associated with traumatic brain injury (TBI) [1]. Approximately 1.5 million Americans sustain a traumatic brain injury annually, with about 50,000 resulting in death and at least 200,000 hospitalizations [2]. About five million Americans live with disability related to brain injury, with nearly 90,000 new injuries resulting in long-term disability per year with an estimated annual cost of nearly \$50 billion [3].

The prevention of secondary sequelae following brain injury is crucial to reduce the significant economic and societal impacts of TBI. This is supported by the dramatic improvement in the post TBI survival rates over the last 25 years [1]; however, acute medical and rehabilitative management, aimed at reducing these secondary injuries, are often hindered by the neurobehavioral complications of brain injury - commonly decreased arousal.

Arousal is the result of communication between the reticulothalamic, thalamocortical and reticulocortical networks. The complex interaction of these pathways relies on both excitatory and inhibitory neurotransmitters to ready the thalamus and cortex for information processing. The degree of cognitive dysfunction after brain injury has been directly correlated to multiple factors: severity of diffuse axonal injury, length of posttraumatic amnesia, and volume of focal cerebral lesions [4]. Pharmacologic treatment of neurobehavioral dysfunction has been shown to accelerate the rate of recovery in patients that have suffered severe TBI [5].

We identified current practice trends related to the use of neurostimulants in patients with decreased arousal secondary to severe brain injury with the goal of better informing the clinical decision-making of physicians caring for patients suffering from TBI.

### Methods

An 8 question unvalidated survey was organized to assess the treatment strategies being utilized in intensive care units to address disorders of attention and arousal following brain injury. The survey was approved by the Institutional Review Board (IRB) of Thomas Jefferson University Hospital and the research committee of the Neurocritical Care Society (NCS). Our sampling population was comprised primarily of neurointensivists, medical intensivists, neurosurgeons and anesthesiologists. The survey, entitled "Clinical Practice Survey: Do you use stimulant medications to improve wakefulness in patients with severe brain injury?", was solicited through e-mail. The survey was available November 15, 2013 - November 29, 2013 and was sent to 1366 NCS members. The survey questions have been reduplicated for publication [Appendix A]: The following information was collected: respondent's training pathway, medications employed, target patient population, time to therapy initiation, duration of therapy, subjective effect, and presence of an institutional protocol. Participants were not restricted to only one answer choice per question. Participants received no form of compensation for completion of this survey. Responses were kept confidential and anonymous. Descriptive statistical analysis was used to examine the data.

### Results

#### Demographics

122 responses were obtained out of 1366 emailed surveys, resulting in a response rate of 9%. A majority of the respondents were neurologists, 55% (67/122). Medical intensivists accounted for approximately 16% of survey respondents. Neurosurgeons and anesthesiologists accounted for 9% and 8% respectively. The remaining 20% were comprised of emergency medicine, general surgery, and physician extenders.

#### Pharmacologic agents

Amantadine, a dopaminergic agent, was the most frequently selected medication for treating arousal disorders among our respondents at 60%. Modafinil was selected by 53%, and methylphenidate by 38% of respondents. Zolpidem, a GABA-A receptor agonist, was selected by 12%. Additionally, 23% selected the "Other" response with write-in answers for levodopa and bromocriptine (Figure 1a).

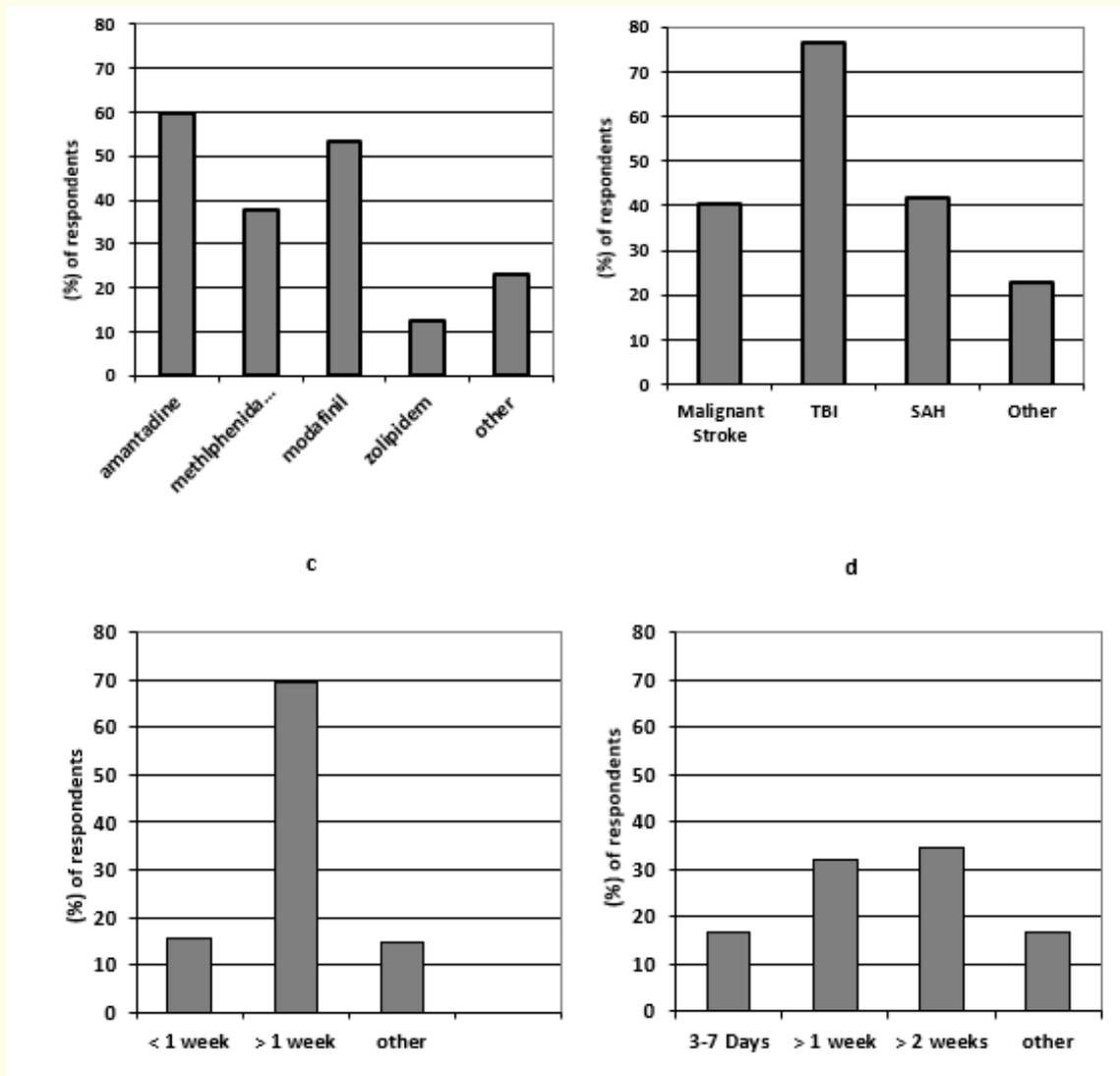
#### Classifications of brain injury

76% of the respondents selected TBI as the primary diagnosis when pharmacologically treating disorders of attention and arousal. 40% of the respondents selected malignant stroke and 42% selected SAH (Figure 1b).

#### Usage

69% initiate treatment to improve wakefulness greater than one week from injury. 16% choose to start medication within the first 7 days. Significant variation was noted in length of therapy. 17% treat for 3-7 days. 32% reported treating for more than a week, whereas

34% treat for more than 2 weeks (Figure 1c and 1d). More than half, 56% would not consider another agent if the initial choice failed to show a clinical improvement. 44% employ an alternate therapeutic agent if their initial choice is not successful in improving mentation.



**Figure 1:** Responses pertaining to the use of medication for the treatment of disorders of attention and arousal following brain injury: (a) Survey medications used to treat disorders of attention and arousal; (b) Types of brain injury; (c) Initiation of treatment from time of brain injury; (d) Length of treatment after initiation of medication.

50% of respondents indicated that medications are efficacious in less than 25% of cases of arousal disturbances following brain injury. 28% felt pharmacologic agents are successful in half or fewer cases. 12% felt agents improved mentation more than half the time. No respondent answered that medication improved wakefulness in greater than 75% of patients.

Notably, only one respondent reported that their home institutions has a guideline in place to direct the usage of pharmacologic agents to improve wakefulness.

### Discussion

Neurobehavioral problems, such as decreased arousal, are common in individuals with severe brain injury [1,4,6-8]. We present results from a society-wide survey evaluating the clinical practice of neurointensivists regarding the treatment of attention and arousal disorders in brain-injured patients. To date, this is the first inquiry of such practice patterns of physicians in neurocritical care.

Disorders of consciousness are a significant impediment to any meaningful rehabilitation following severe brain injury. Neuro-stimulant usage following brain injury may improve a patient's rehabilitation potential [9]. Most extant literature concerns patients afflicted with TBI [5,9-12]; however, our survey found that many physicians are using stimulants in patients with malignant MCA strokes and high grade SAH. A paucity of literature is available regarding stimulant use in these pathologies and further clinical studies are warranted.

Following severe brain injury, disturbed cognition is the most commonly cited problem reported by patients and their caregivers, even years after brain injury [8]. Behavioral derangement following brain injury is a complex, multifactorial disease process and may contribute more to disability than the physical impairment sustained by patients [7]. A variety of biochemical alterations have been reported in the milieu of the brain following injury, with recovery being marked by restoration of dopamine and norepinephrine neurotransmitters from inadequate post-injury levels [4].

Neuro-stimulants function via various mechanisms to enhance neurotransmission in the organs involved in attention and arousal [10]. Neuro-stimulants such as methylphenidate and dextroamphetamine work primarily as sympathomimetics, indirectly causing increased norepinephrine and dopamine receptor stimulation via reuptake inhibition and increased synaptic vesicle binding [13]. Amantadine has effects on multiple neurotransmitters, increasing levels of dopamine (both pre- and post-synaptic), norepinephrine, and serotonin [14]. In the case of modafinil, there is both histaminergic activity as well as inhibition of dopamine reuptake [13]. Bromocriptine is a selective D-2 receptor agonist with a preponderance of receptors in the basal ganglia, striatum, hippocampus as well as thalamus, which includes projections to the nucleus accumbens and pre-frontal cortex [15].

Our survey showed that a majority of practitioners use amantadine followed closely by modafinil. It is interesting to note that 45% of respondents reported initiating a second agent if the first choice medication was thought not to have a measurable clinical response. With the exception of amantadine in the setting of severe TBI (as proposed by Giacino [5,10]), clinical data on the use of other agents are limited to either small sample size trials or observational/retrospective studies [5,9,11].

Most survey respondents (70%) initiate neuro-stimulants one week after brain injury. This practice appears to be consistent with the current available literature [9-12]. Conversely, Giacino enrolled brain injured patients 4-16 weeks after non penetrating injury and reported accelerated pace of functional recovery with the use of amantadine [10]. Approximately 16% of respondents start stimulants less than a week from injury. It remains to be determined whether or not earlier initiation of stimulants improves functional outcomes.

### Limitations

The sample size of respondents is relatively small: 122 respondents participated out of 1366 inquiries. In addition, portions of data rely are subjected to recall bias, for example, clinical response to treatment. Survey responses may also have been influenced by unmeasured variations in types of patients under the respondents care: some centers may see a higher volume of TBI patients whereas other centers primarily treat neurovascular disease.

### Conclusion

A variety of pharmacologic agents are being utilized to treat disorders of attention and arousal in neurological intensive care units following severe brain injury. Amantadine is most commonly used. The efficacy of pharmacologic therapy remains unclear, and accordingly almost no institutional protocols were reported. Further clinical trials are required to elucidate the role of stimulants in brain-injured patients.

## Disclosure

James Peoples MD, Alejandro J. Lopez DO, Kristofer Feeko DO, Lauren Ng MD MPH, Michelle Ghobriel MD, Omar Shah MD Matthew Vibbert MD, Jacqueline Urtecho MD, Jack Jallo MD PhD, Carissa C. Pineda, MD, Diana Tzeng MD, Rodney Bell MD, Fred Rincon MD MSc, Barak Bar MD and M. Kamran Athar MD declare that they have no conflict of interest.

## Appendix 1:

1. Of the following pharmacologic agents, please select the ones you have used most often to improve “wakefulness” in your brain injury patients?
  - a. Methylphenidate
  - b. Amantadine
  - c. Modafinil
  - d. Zolpidem
  - e. Other
2. At what time interval from injury are you initiating treatment to attempt to improve wakefulness?
  - a. < 1 week
  - b. > 1 week
3. How long are you treating for?
  - a. 3 - 7 days
  - b. 1 week
  - c. > 1 week
  - d. > 2 weeks
  - e. Other
4. Have you ever initially tried one medication, and then started another after the first did not have a measurable clinical improvement?
  - a. Yes
  - b. No
5. What types of brain injury patients do you primarily see in your current practice?
  - a. SAH
  - b. Malignant CVA
  - c. TBI-DAI-Trauma
  - d. Other
6. In your experience, please approximate the percentage of your patients that have some form of increased wakefulness when pharmacological agents are employed?
  - a. 0 - 25%
  - b. 25 - 50%
  - c. 50 - 75%
  - d. 75 - 100%
7. Does your institution have a protocol or practice guideline for the use of stimulants in severe brain injury?
  - a. Yes
  - b. No

8. What training pathway did you undertake on your way to the practice of neurocritical care?
  - a. Neurology
  - b. Neurosurgery
  - c. Medicine
  - d. Anesthesiology
  - e. Other

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Volume 12 Issue 1 January 2020

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