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Stimulant Therapy in Acute Traumatic Brain Injury: Prescribing Patterns and Adverse Event Rates at Two Level 1 Trauma Centers

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Abstract

Background/objective: Pharmacological stimulant therapies are routinely administered to promote recovery in patients with subacute and chronic disorders of consciousness (DoC). However, utilization rates and adverse drug event (ADE) rates of stimulant therapies in patients with acute DoC are unknown. We aimed to determine the frequency of stimulant use and associated ADEs in intensive care unit (ICU) patients with acute DoC caused by traumatic brain injury (TBI).

Methods: We retrospectively identified patients with TBI admitted to the ICU at two Level 1 Trauma Centers between 2015-2018. Patients were included if they were stimulant-naïve at baseline and received amantadine, methylphenidate, or modafinil during ICU admission. Stimulant dose reduction or discontinuation during ICU admission was considered a surrogate marker of an ADE. Targeted chart review was performed to identify reasons for dose reduction or discontinuation.

Results: Forty-eight of 608 TBI patients received pharmacological stimulant therapy (7.9%) during the study period. Most patients were diagnosed with a severe TBI at presentation (60.4%), although stimulants were also administered to patients with moderate (14.6%) and mild (25.0%) TBI. The median time of stimulant initiation was 11 days post-injury (range 2–28). Median Glasgow Coma Scale score at the time of stimulant initiation was 9 (range 4–15). Amantadine was the most commonly prescribed stimulant (85.4%) followed by modafinil (14.6%). Seven patients (14.6%) required stimulant dose reduction or discontinuation during ICU admission. The most common ADE resulting in therapy modification was delirium/agitation (n=2), followed by insomnia (n=1), anxiety (n=1), and rash (n=1); the reason for therapy modification was undocumented in two patients.

Conclusions: Pharmacological stimulant therapy is infrequently prescribed but well-tolerated in ICU patients with acute TBI at Level 1 Trauma Centers. These retrospective observations provide the basis for prospective studies to evaluate the safety, optimal dose range, and efficacy of stimulant therapies in this population.

Keywords

pharmacological stimulant; consciousness; coma; traumatic brain injury; intensive care unit

Introduction

For patients with traumatic brain injury (TBI) admitted to the intensive care unit (ICU), early recovery of consciousness is a key prognostic indicator of long-term functional recovery^{1,2} and a critical determinant of access to rehabilitative care.³ Patients who remain unconscious on bedside neurological examination are often believed to have a poor prognosis and are more likely to die in the ICU due to withdrawal of life-sustaining therapy.⁴ It is unknown whether therapies administered in the ICU may accelerate early recovery of consciousness, and if so, whether such therapeutic acceleration of recovery may be linked to better long-term outcomes.

Multiple therapies have been tested in the subacute (weeks to months) and chronic (months to years) stages of recovery from TBI, including pharmacological stimulant therapy,⁵ transcranial direct current stimulation,⁶ and central thalamic deep brain stimulation.⁷ Given the risks associated with invasive procedures and the feasibility limitations associated with device-based therapies, pharmacological stimulants are a practical therapeutic option for utilization in the ICU setting. Despite level 1 evidence supporting subacute administration of amantadine to accelerate recovery of consciousness after TBI,⁸ there are no data regarding optimal stimulant selection in the ICU setting.

Pharmacological stimulant therapy is now increasingly being used in the ICU off-label for the treatment of disorders of consciousness (DoC), but few studies have tested the safety or efficacy of pharmacological stimulant therapy in this setting.^{9–15} Amantadine, methylphenidate, and modafinil are therapeutic stimulant options, with varying mechanisms of action that all potentially upregulate cortical function and promote recovery of consciousness.¹⁶ Common side effects of stimulant therapy include behavioral alterations, such as insomnia, hallucinations, irritability, anxiety, psychosis, agitation, and delirium.¹⁷

Critically ill patients with acute TBI may be at higher risk of medication-induced adverse effects, as compared to patients with subacute and chronic TBI. The objective of this study is to examine prescribing patterns and adverse event rates for stimulant therapy in patients with TBI admitted to the ICUs at two Level 1 Trauma Centers.

Methods

Subject Selection and Study Design

We performed a retrospective analysis of patients with acute TBI admitted to either the Neurosciences or Surgical ICUs at two Level I Trauma Centers in Boston, MA, USA – Massachusetts General Hospital and Brigham and Women's Hospital. The study period evaluated patients admitted to Massachusetts General Hospital from April 2016 to February 2018 and Brigham and Women's Hospital from June 2015 to February 2018, after implementation of a new electronic medical record system. We included patients if they were 18 years of age and received amantadine, methylphenidate, or modafinil during ICU admission for TBI. A medication dispense report for inpatient stimulant use was used to identify patients administered stimulant therapy with a concurrent diagnosis of TBI. We used an established screening database to identify the total number of TBI patients admitted to an ICU at Massachusetts General Hospital during the study period. We used the Partners Healthcare Research Patient Data Registry to obtain an approximation of the total number of TBI patients admitted to an ICU at Brigham and Women's Hospital during the study period, using International Classification of Diseases Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes. Patients were excluded if they were prescribed amantadine, methylphenidate, or modafinil prior to admission. Institutional Review Board approval was obtained prior to study initiation, and consent was waived.

Adverse Drug Event Definition and Characterization

Our primary outcomes were stimulant prescribing patterns in acute TBI and stimulant-related adverse drug events (ADEs) during ICU admission. Secondary outcome measures were stimulant-related ADEs during hospitalization, adjunct anti-psychotic and sleep aid medication use, and change in Glasgow Coma Scale (GCS) score during stimulant therapy while in the ICU. Patients were followed until hospital discharge or death.

We used the hospitals' electronic medical record system to identify patients who were administered a stimulant medication during the study period. Stimulant dose reduction or discontinuation was used as a surrogate marker for an ADE attributed to stimulant therapy, consistent with prior retrospective ADE studies.^{18,19} Targeted chart review was performed to confirm and characterize the type of ADE. The term agitation was used to characterize patients for whom agitation or hyperactive delirium was reported in the patient chart. The Naranjo ADE probability scale was utilized to assess the likelihood that a stimulant caused the ADE.²⁰ Patients were assessed for resolution of ADE for up to five days after dose reduction or discontinuation.

Chart review was performed to collect baseline demographics and clinical characteristics, including variables with potential to confound the neurologic exam, such as sedative

administration within 6 hours prior to stimulant initiation, opioid or sedating antiseizure drug administered within 12 hours of initiation, seizure activity on electroencephalogram within the previous 24 hours, hyperosmolar therapy (mannitol or hypertonic saline) within 12 hours of stimulant initiation, and presence of an intracranial bolt, external ventricular drain or ventriculoperitoneal shunt at the time of stimulant initiation. Glasgow Coma Scale and Confusion Assessment Method for the ICU were retrospectively collected per nursing assessments documented in the medical record. Anti-psychotic medications screened for administration during stimulant therapy included haloperidol, quetiapine, olanzapine, ziprasidone, aripiprazole, and risperidone, any of which may be used for the treatment of acute agitation or delirium. Sleep-aid medications screened for administration during stimulant therapy included melatonin, ramelteon, trazodone, zolpidem, and benzodiazepines. All analyses were performed using descriptive statistics.

Results

Demographics and Clinical Characteristics

We identified 48 patients with acute TBI who were initiated on a stimulant therapy during ICU admission (Figure 1), representing 7.9% (48/608) of TBI patients admitted to the ICU during the study period. At Massachusetts General Hospital, 7.1% (75/352) of patients were prescribed a stimulant during ICU admission compared to 9.2% (23/249) of patients at Brigham and Women's Hospital. The median age was 58 years and the most common etiology of TBI was a fall (45.8%; 22/48) followed by motor vehicle accident (35.4%; 17/48) (Table 1). Most patients were diagnosed with a severe TBI at presentation (60.4%; 29/48), although stimulants were also administered to patients with moderate (14.6%; 7/48) and mild (25.0%; 12/48) TBI. All 12 patients with mild TBI on presentation had intracranial hemorrhages on head computed tomography (i.e complicated mild TBI). Seven of 12 (58.3%) of patients had a GCS < 13 at the time of stimulant initiation. In three patients with subdural hemorrhages, stimulant therapy was initiated after treatment of status epilepticus (n=2) and frequent epileptiform discharges (n=1), at which time GCS ranged from 4 – 10.

Pharmacological Stimulant Prescribing Patterns

Most ICU patients were initiated on amantadine (85.4%; 41/48), followed by modafinil (14.6%; 7/48). Stimulant therapy was initiated at a median of 11 days after admission (Table 2). No patients were treated with methylphenidate as initial therapy. Low arousal was the most common documented indication for stimulant therapy in 72.9% (35/48) of patients, followed by inattention (2.1%; 1/48), and other (8.3%; 4/48). Indication was not documented in 16.7% (8/48). In patients with mild TBI on admission, 75% (9/12) were prescribed a stimulant for low arousal, 8.3% (1/12) for inattention, 8.3% (1/12) for intermittent apnea, and 1 patient's indication was not documented. The median initial starting dose was 100 mg/day for both amantadine and modafinil, which was increased to a median amantadine dose of 200 mg/day and modafinil 150 mg/day by hospital discharge. Twenty (41.7%) patients were on concurrent opioid therapy and 26 (54.7%) received antiseizure medications at the time of stimulant initiation. Thirty-four patients (70.8%; 34/48) were discharged from the hospital on a stimulant medication.

Stimulant-Related Adverse Drug Events

Seven patients (14.6%) required stimulant dose reduction or discontinuation while in the ICU (Table 2). Five patients on amantadine (12.2%; 5/41) and two patients on modafinil (28.6%; 2/7) experienced a stimulant-related ADE during ICU admission. The most common ADE resulting in therapy modification was agitation (n=2), followed by insomnia (n=1), anxiety (n=1), and rash (n=1) (Figure 2). The reason for therapy modification was undocumented in two patients. Ten patients (20.8%) required stimulant dose reduction or discontinuation during their hospitalization, with an additional two patients on amantadine experiencing agitation and one patient on amantadine experiencing urinary retention after transfer from the ICU to an acute care unit. The Naranjo score indicated a possible (range 1–4) association with stimulant exposure in four patients and doubtful (range 0) association in three patients whose events occurred while in the ICU. For all three events that occurred after transfer to the acute care unit, the Naranjo score indicated a possible association of the event with stimulant exposure.

A sleep aid medication was concurrently administered in 19 (39.6%) patients prescribed stimulant therapy and an antipsychotic medication in 13 (27%) patients during the hospitalization. Quetiapine was prescribed in all 13 patients, of whom 5 patients received haloperidol (4 patients during the evening and one patient during the day). Confusion assessment method for the ICU was positive for delirium at least once during stimulant therapy in 18 (37.5%) patients.

Clinical Outcomes

The median GCS at stimulant initiation was 9, which increased by a median of 1 (IQR 0, 3) by ICU discharge and by 3 (IQR 0, 4) by hospital discharge (Table 3). Median ICU length of stay was 17.5 days (IQR 13.4, 22.3) and hospital length of stay 23.2 days (IQR 17.8, 31.7).

Discussion

In this retrospective study of pharmacologic stimulant use at two Level 1 Trauma Centers, we found that stimulants are infrequently administered in the ICU to promote recovery in patients with acute TBI. Between 2015 and 2018, 7.9% of 608 patients with acute TBI were initiated on stimulant therapy. Despite low utilization, stimulant therapy was well tolerated, with ADEs occurring in 14.6% of patients during ICU admission. The most common ADE was agitation. Notably, no ADE was determined to be of a probable or definite association with stimulant use for causality.

Amantadine was the most commonly prescribed stimulant in our study, followed by modafinil and methylphenidate. Amantadine acts as a dopamine agonist pre-synaptically by increasing dopamine release and delaying dopamine reuptake, along with post-synaptic effects on dopamine receptors.¹⁷ In addition, amantadine exhibits N-methyl-D-aspartate channel antagonist properties. Modafinil is thought to inhibit dopamine and norepinephrine transporters to increase synaptic catecholamine levels and produces indirect effects on extracellular levels of gamma aminobutyric acid, serotonin, glutamate, histamine, and orexin.²¹ Methylphenidate inhibits pre-synaptic reuptake of catecholamines and stimulates

the release of dopamine and norepinephrine.²² Stimulants thus act upon subcortical dopaminergic neurons involved in arousal and cortical neurons that mediate attention, but the relative efficacy of stimulant use for these two applications in the ICU setting is unknown. In our study, the most common indication for prescribing a stimulant was to treat low arousal (72.9%), followed by inattention (2.1%). We acknowledge that these utilization data are inherently a reflection of the prescribing practices of the ICU clinicians. Nevertheless, prescribing rates and indications for therapy were similar between the two institutions included in this study.

With respect to the safety of stimulant use in ICU patients with acute TBI, our findings are consistent with and build upon those of a small number of studies that have examined stimulant-related ADEs in this population.^{9–15} Meythaler and colleagues performed a double-blind randomized controlled trial of amantadine to improve neurorecovery in patients with TBI-associated diffuse axonal injury, reporting no serious ADEs and no side-effect related dose adjustments in 15 patients treated with amantadine.¹⁵ Prior studies reported central nervous system side effects, difficulty urinating, and rash.¹⁷ While seizures have been reported in patients with TBI-related DoC, incidence rates were comparable to placebo in randomized trials.^{8,11,15} Similarly, ADEs in our population were minor and not life-threatening. Furthermore, our Naranjo score analysis indicated that ADE association with stimulant exposure was only possible or doubtful, raising the possibility that the stimulant medications may not have been directly responsible for the side effects that were documented in the medical record. Nevertheless, it is important to highlight that the field of stimulant use in ICU patients is just recently emerging and that this population is particularly vulnerable to adverse drug events. Acute changes in organ function due to critical illness and the use of interacting medications can lead to alterations in pharmacokinetics.²³ Additionally, it is possible that dopaminergic stimulation could exacerbate glutamate-mediated excitotoxicity in acute TBI. However, evidence from rat neuronal models suggests that dopamine may be protective against such excitotoxicity.²⁴ Thus, larger prospective studies are needed to more comprehensively characterize stimulant safety in ICU patients.

Interestingly, we found that antipsychotic medications were frequently administered concurrently with stimulants. Approximately 16.7% of patients were administered an antipsychotic, such as quetiapine, to treat nighttime agitation or insomnia and 10.4% were administered an antipsychotic during the day while on stimulant therapy. As needed haloperidol was administered in 5 patients, one of whom was treated during the daytime. Antipsychotic mechanism of action is thought to be primarily due to dopamine D₂ receptor antagonism,²⁵ with haloperidol resulting in higher rates of D₂ occupancy²⁶ and a longer duration of D₂ blockade²⁷ than quetiapine.^{28,29} Competing dopaminergic blockade may occur in patients who are receiving concurrent stimulant and antipsychotic therapy. The reduction in benefit of stimulant therapy is most concerning in patients receiving longer acting agents such as haloperidol and olanzapine (half-life elimination 14–37 hours and 30 hours, respectively) or daytime quetiapine administration (half-life elimination 6 hours).^{30–32}

Our findings suggest that future studies of pharmacologic stimulants in ICU patients with acute TBI should focus on agitation as a potential side effect. Agitation was the most common adverse event observed in our study. Similarly, a recent study of neurocritically ill patients with TBI showed a potential association between amantadine use and increased agitation compared to the standard of care.⁹ However, agitation and delirium are common in ICU patients, with rates up to 43% in neurocritically ill patients³³ and 46.3 – 69.4% in patients with TBI.^{34,35} ICU delirium is associated with prolonged ICU length of stay, hospital length of stay, and worse functional independence and cognition, all of which are likely to be present in patients with DoC due to acute severe TBI. Additionally, elucidating a potential link between stimulants and ICU delirium in future studies will be inherently challenging, due to limitations of currently available assessment tools, such as the Confusion Assessment Method for the ICU or Intensive Care Delirium Screening Checklist. These tools do not distinguish hypoactive or hyperactive delirium from decreased level of consciousness or agitation related to a brain injury.³³ In our study, for patients whose agitation led to dose reduction or discontinuation while in the ICU, symptoms were present prior to the initiation of stimulant therapy and discontinuation of therapy did not lead to symptom resolution within five days. In the two patients who experienced agitation after transfer to the acute care unit, only one patient's symptoms resolved shortly after stimulant discontinuation. Therefore, while stimulant use may have been a contributing factor, it is likely that other factors played a more defining role in the development of these events.

We propose that stimulant therapy administration times, dosage, and sleep management options should be optimized prior to scheduled antipsychotic administration to minimize competing dopaminergic activity. While the optimal timing for stimulant medication administration is currently unknown, earlier administration of afternoon doses may allow for optimization of sleep wake cycle and reduced need for night time sleep-aid medications or antipsychotics. In our study, stimulant administration in the evening was associated with night time agitation in one patient. At our institutions, stimulant medications are commonly administered between 06:00 – 09:00 for once daily administration and 12:00 – 14:00 for afternoon administration of twice daily medications.

Limitations

Given the retrospective design of our study, the primary indication for stimulant therapy was not reported in standardized fashion. As such, we were unable to comprehensively evaluate the distribution of indications for stimulant therapy. Additionally, a small sample received methylphenidate or modafinil therapy. Therefore, the adverse effect profile for these medications may not have been adequately captured in this patient population. While dose reduction or discontinuation was used as a surrogate ADE marker, it is possible that ADEs may have been present but undetected by treating clinicians during ICU or hospital admission. It is also possible that minor ADEs were recognized by clinicians but did not require therapy modification, and thus were not detected by our methodology for identifying stimulant-related ADEs. Additionally, patients evaluated in our study were up-titrated more quickly compared to the 4-week titration schedule used in a previous trial,⁸ and the impact of rapid up-titration on the frequency of ADEs is unknown. While agitation was the most commonly reported ADE in our study, given the complexity of assessing delirium in ICU

patients with TBI, it is difficult to ascertain whether stimulant use increases the risk for agitation or delirium resulting in need for antipsychotic use. Finally, we were unable to evaluate the impact of stimulant therapy on clinical outcomes such as ICU and hospital length of stay given the small sample size and limited statistical power. Future studies with larger sample sizes are needed to account for the multitude of neurologic and medical confounders that can affect these outcome measures in unpredictable ways. ICU and hospital length of stay data in our patients who received stimulants should be interpreted with caution.

Conclusions

In conclusion, stimulant therapy is infrequently prescribed in patients with acute TBI during ICU admission and is associated with a low incidence of ADEs, with the most common ADE being agitation. This retrospective safety work provides the basis for prospective studies to further assess the safety and efficacy of pharmacological stimulant therapy for patients with TBI in the ICU.

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Figure 1: Stimulant Therapy in Patients with Traumatic Brain Injury

Figure 2: Stimulant Dose Reduction or Discontinuation Attributed to Adverse Drug Events

Table 1:**Patient Demographics and Clinical Characteristics**

Baseline Characteristics – no.(%)	N=48
Age, years ^a	58 (29, 73)
Female sex	15 (31.3)
BMI, kg/m ^{2a}	24.9 (21.9, 28.4)
Transferred from outside hospital	34 (70.8)
Type of injury	
Fall	22 (45.8)
Motor vehicle accident	17 (35.4)
Pedestrian hit by car	3 (6.3)
Sports injury	2 (4.2)
Gun shot wound	2 (4.2)
Assault	1 (2.1)
Unknown etiology	1 (2.1)
TBI severity	
Mild TBI, GCS 13 – 15	12 (25)
Moderate TBI, GCS 9 – 12	7 (14.6)
Severe TBI, GCS < 9	29 (60.4)
GCS score at presentation ^a	6.5 (4, 12.25)
Patient Characteristics at time of stimulant initiation – no.(%)	
GCS at stimulant initiation ^a	9 (7,11)
Time from admission to stimulant initiation–days ^a	11 (8, 17)
Mechanical ventilation	
ETT	13 (27.1)
Tracheostomy	18 (37.5)
Opioid medication concurrent use	20 (41.7)
Sedative medication concurrent use	7 (14.6)
Sedating antiseizure medication concurrent use	26 (54.2)
Ongoing seizure activity	0 (0)
EVD/VP Shunt	8 (16.7)
Hyperosmolar therapy	2 (4.2)

^a data presented as median (interquartile range)

BMI – body mass index; ETT – endotracheal tube; EVD – external ventricular drain; GCS – Glasgow Coma Scale; TBI – traumatic Brain Injury; VP – ventriculoperitoneal

Table 2:**Stimulant Prescribing Patterns and Stimulant-Related Adverse Drug Events**

Primary Outcome Measures – no. (%)	N=48
Initiation stimulant dose, mg/day ^a	
Amantadine (n=41)	100 (100, 200)
Modafinil (n=7)	100 (100, 150)
Methylphenidate (n=0)	-
Switched to alternative stimulant	
Amantadine	1 (2.1)
Modafinil	0 (0)
Methylphenidate	1 (2.1)
Discharge stimulant dose, mg/day ^a	
Amantadine (n=31)	200 (175, 250)
Modafinil (n=2)	150 (125, 175)
Methylphenidate (n=1)	5
Time from stimulant initiation to ADE, days ^a	5.5 (4, 7.75)
ADE during ICU admission	7 (14.6)
ADE during hospitalization	10 (20.8)
Naranjo probability scale score ^b	3 (0, 4)

^a data presented as median (interquartile range)

^b data presented as median (range)

ADE – adverse drug event; ICU – intensive care unit

Table 3:**Patient Clinical Course**

Clinical Outcomes – no. (%)	N=48
GCS on ICU discharge ^a	11 (8, 14)
Change in GCS from initiation to ICU discharge ^a	1 (0, 3)
GCS on hospital discharge ^a	12.5 (9, 14)
Change in GCS from initiation to hospital discharge ^a	3 (0, 4)
Sleep aid medication administered	19 (39.6)
Antipsychotic medication administered	
Administered at night only	8 (16.7)
Administered during the day	5 (10.4)
CAM-ICU positive during stimulant therapy	
No	16 (33.3)
Yes	18 (37.5)
No documentation	14 (29.2)
Duration of CAM Positive, days ^a	2.4 (1.2, 6.0)
Tracheostomy placed	26 (54.2)
Duration of ETT placement, days ^a	9.7 (5.4, 14.1)
ICU length of stay, days ^a	17.5 (13.4, 22.3)
Hospital length of stay, days ^a	23.2 (17.8, 31.7)
In-hospital mortality	6 (12.5)

^a data presented as median (interquartile range)

CAM-ICU – Confusion assessment method for the ICU; ETT endotracheal tube; GCS – Glasgow Coma Scale; ICU – intensive care unit