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A descriptive analysis of pharmacological management of aggression and/or agitation in patients with traumatic brain injury in a Southwest Virginia inpatient population

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Abstract

What Is Known and Objective: Traumatic brain injury (TBI) is a major cause of disability, and it has been associated with agitation and aggression. In a previous study, we reviewed the literature to identify evidence-based pharmacological agents for treatment of agitation in TBI. Based on the results of our previous study that summarizes the findings of several systematic reviews, the use of haloperidol and benzodiazepines is not supported by the available evidence while the use of amantadine, beta blockers, antiepileptics and methylphenidate is supported by the limited available evidence. In this study, we describe the psycho-pharmacological agents that were administered to patients with agitation and/or aggression in the context of TBI in inpatient facilities of a private, non-profit health care system in southwest Virginia. We will also compare the psycho-pharmacological agents ordered before and after psychiatric consultation.

Methods: Adult patients who were admitted to Carilion Clinic's inpatient facilities from March 30, 2013, to March 30, 2018, had a diagnosis of TBI, and received psychiatric consultation for agitation and/or aggression were enrolled in this study. A retrospective review of electronic medical records was conducted by researchers and data were collected on the following measures: ordered psycho-pharmacological agents, frequency, dosing and duration of orders, whether each administered psycho-pharmacological agent was started before or after psychiatric consultation, and psycho-pharmacological agents prescribed upon discharge.

Results and Discussion: About 68% of patients were started on benzodiazepines and/or typical antipsychotics and 23% of patients were subsequently discharged on these medication categories. Only 23% of patients were ordered to receive medications supported by the evidence such as amantadine, beta blockers or antiepileptics. The percentage of patient-days with an order to receive typical antipsychotics significantly decreased following psychiatric consultation ($p = 0.0056$), but the percentage of patient-days with an order to receive benzodiazepines significantly increased

following psychiatric consultation ($p = 0.0001$). This finding remained statistically significant after excluding patients with active or unclear alcohol/benzodiazepine withdrawal ($p < 0.0001$).

What Is New and Conclusion: This study demonstrates the widespread use of typical antipsychotics and benzodiazepines in the management of agitation in TBI and the importance of multidisciplinary collaboration, research and education of providers to improve patient care.

KEYWORDS
agitation, traumatic brain injury

1 | WHAT IS KNOWN AND OBJECTIVE

According to the Centres for Disease Control, traumatic brain injury (TBI) is broadly defined as a disruption in the normal function of the brain that can be caused by a bump, blow or jolt to the head, or penetrating head injury.[1] There are ~50 million new cases of TBI worldwide every year and about 3.5 million in the United States alone.[2] Behavioural disorders often ensue following a TBI which are often devastating for both the individual and their family system. For instance, individuals with TBI can become irritable, agitated and aggressive leading to possible loss of employment, relationships, domestic violence and incarceration in its more severe form.[1,3,4] Mental health professionals often encounter TBI patients in the hospital setting and are commonly called upon to guide treatment of their behavioural disturbances. While addressing potential organic etiologies of agitation and behavioural interventions are considered the first line of treatment for agitation or aggression in the context of TBI, acute pharmacological management is often necessary to ensure safety for both the patient and health care team. However, there are limited guidelines for this treatment.

In a previous study,[5] we reviewed the literature to identify evidence-based pharmacological agents for the treatment of agitation in TBI. Based on the results of our previous study that summarizes the findings of several systematic reviews,[6–15] the use of haloperidol and benzodiazepines is not supported by the available evidence while the use of dopaminergic agents (amantadine and methylphenidate), beta blockers (propranolol and pindolol) and antiepileptics (valproic acid) is supported by the limited available evidence. Our findings were in line with the recommendations of the international group of researchers and clinicians (known as INCOG) against the use of haloperidol for agitation in the context of TBI[16] and preclinical data suggesting that haloperidol can hinder neurocognitive recovery following TBI.[17–20] One clinical question that may follow this information, would be "What agent(s) can be used for acute agitation in the context of TBI?". Currently, there is one small study conducted in the outpatient setting that supports the use of olanzapine for the treatment of agitation in the context of TBI.[21] In the absence of better evidence, we recommended atypical antipsychotics (and particularly olanzapine) as a practical alternative(s) to typical antipsychotics and benzodiazepines for as-needed management of acute agitation.

Despite this data, several studies[22–24] indicate that typical antipsychotics with strong dopamine antagonism (such as haloperidol) and benzodiazepines can be frequently used in the management of agitation and/or aggression in patients with TBI. Moreover, decisions regarding the management of agitation in TBI are frequently made in an interdisciplinary environment and there is limited information on how different disciplines affect patient care.

The primary objective of this study is to describe the psychopharmacological agents administered to patients with agitation and/or aggression in the context of TBI in inpatient units of Carilion Clinic. Secondary objectives include evaluating whether there is a difference in prescription patterns before and after psychiatric consultation, evaluating whether the length of stay is different based on whether a patient receives an evidence-based medication for agitation in TBI or not, and evaluating whether the frequency of agitated days is different before and after starting an evidence-based medication.

2 | METHODS

2.1 | Study population

This study included adult patients admitted to Carilion Clinic's inpatient facilities from March 30, 2013, to March 30, 2018, with a diagnosis of TBI who received psychiatric consultation for agitation, aggression or behavioural disturbance during admission. Children (individuals <18-years-old) were excluded and there was no maximum age for inclusion in this study. Carilion Clinic is a private, non-profit health care system located in southwest Virginia and mostly serves Central and southwestern Virginia and Southern West Virginia. Clarion Clinic's inpatient facilities provide acute inpatient care and inpatient rehabilitation and include teaching and non-teaching hospitals.

To identify relevant encounters, inpatient hospitalizations with the following characteristics were selected: (1) an admission and/or discharge diagnosis of TBI and (2) at least one psychiatric consultation during the course of admission. The 'reason for consult' section of psychiatric consult orders were searched for agit*, aggress*, behav*

and/or angry. The results were reviewed independently by two researchers for meeting the inclusion/exclusion criteria. Disagreements were resolved by discussion and consensus. All patients that met the inclusion criteria and lacked the exclusion criteria were included in the study. This study was not funded.

2.2 | Data collection/extraction

Researchers reviewed the medical records of the included patients retrospectively to extract the following information: age, gender, race/ethnicity, time since index trauma, severity of TBI, length of admission, comorbid conditions, acute alcohol or benzodiazepine withdrawal, timing and frequency of agitation, ordered psychopharmacological agents, frequency, dosing and duration of orders, whether each administered psychopharmacological agent was prescribed before admission, psycho-pharmacological agents prescribed upon discharge and timing and frequency of psychiatric consultation and follow up.

Agitated days were defined by at least one report of agitation during the day in the medical records. The severity of TBI was defined based on the classification of Veterans Affairs/Department of Defence clinical practice guidelines for management of concussion/mild TBI.[25] The presence/absence of acute alcohol or benzodiazepine withdrawal was determined based on results of psychiatric evaluations and/or documentation of recent alcohol/benzodiazepine use in medical records. The cases without clear documentation of recent alcohol/benzodiazepine use were classified as unclear. Data were divided in half and assigned to two researchers for extraction. Data points without ambiguity were not extracted in duplicates. Questions about data points were resolved through discussion and consensus.

Data were extracted and managed using REDCap electronic data capture software which is approved by Carilion Clinic's institutional review board (IRB).[26,27] This software is firewall protected, and compliant with the health insurance portability and accountability act (HIPAA). De-identified data were then exported from this software into a secure network directory for statistical analysis with SAS. All procedures of this study were approved by Carilion Clinic's IRB.

2.3 | Statistical analysis

Data were analysed using SAS 9.4 software. Measures of central tendency and variation were used to describe numeric variables and frequencies and percentages were used for categorical variables. Means and standard deviations (SD) were reported for variables with normal distribution and medians and interquartile ranges (IQR) were reported for variables with skewed distribution.

Psycho-pharmacological agents were summarized into the following groups: benzodiazepines (except for midazolam as this medication is often used as anaesthetic for procedures), typical antipsychotics, atypical antipsychotics, valproic acid (including valproate, sodium valproate and divalproex), carbamazepine, amantadine, beta blockers (including only propranolol and pindolol that are used for management of agitation in TBI) and methylphenidate. Based on the available evidence[6–15] and the researchers' previous study,[5] psycho-pharmacological agents were further summarized into three larger groups: non-recommended for as-needed management of acute agitation in TBI (typical antipsychotics and benzodiazepines), recommend for as-needed management of acute TBI (atypical antipsychotics), and recommended for scheduled (preventative) management of agitation in TBI (amantadine, beta blockers, methylphenidate, valproic acid and carbamazepine). These medication groupings are summarized in Table 1. Data were reported for psychopharmacological agents that were started during admission. Percentages of patients that were started on each category of medications and percentages of patients who were discharged on each category of psychopharmacological agents were reported. The percentage of admission days that each patient was ordered to receive each category of medications was calculated. McNemar's test was used to evaluate whether there was a significant difference in the percentage of admission days each medication group was ordered before and after psychiatric consultation. Paired sample *t* tests were used to compare the frequency of agitated days before and after initiation of recommended scheduled medications. Patients were divided into two groups based on whether they had received recommended medications (for scheduled and/or as-needed use) at any point during admission and a Mann–Whitney *U* test was used to compare length of stay between the two groups.

TABLE 1 Summary of medication groupings

As-needed management of acute agitation in TBI	
Non-recommended	Typical antipsychotics, benzodiazepines
Recommended[a]	Atypical antipsychotics (especially olanzapine) as practical alternatives
Scheduled management of agitation in TBI	
Recommended	Amantadine (especially in the context of chronic TBI), propranolol (particularly in the context of acute TBI), methylphenidate and antiepileptics

Note: Please see researchers' previous work[5] for data that supports the strength of each recommendation.
[a]As practical alternative(s) based on limited evidence.

3 | RESULTS

The initial electronic record search based on admission/discharge diagnosis of TBI and psychiatric consultation identified 298 visits for 289 unique patients. Following the examination of the 'reason for consult' section of psychiatric consult orders and review by researchers for meeting inclusion/exclusion criteria, a total of 31 patients were identified.

The baseline characteristics of the patients are summarized in Table 2. As demonstrated in this table, the average age of our sample was 50.13 years ($SD = 17.21$), and the majority of patients were male

TABLE 2 Baseline characteristics

Variable	All patients	Patients receiving recommended medications	Patients not receiving recommended medications
Sample Size	31	19	12
Age	Mean (*SD*) = 50.13 (17.21)	Mean (*SD*) = 51.21 (16.54)	Mean (*SD*) = 48.42 (18.85)
Gender	9 Female, 22 male	4 Female, 15 male	5 Female, 7 male
Race	30 Caucasian, 1 African American	18 Caucasian, 1 African American	12 Caucasian
LOS	Median (IQR) = 10.99 (4.89, 26.12)	Median (IQR) = 17.07 (7.09, 26.77)	Median (IQR) = 7.93 (3.38, 17.50)
TBI severity	8 Mild, 13 moderate, 6 severe, 4 unknown	3 Mild, 9 moderate, 5 severe, 2 unknown	5 Mild, 4 moderate, 1 severe, 2 unknown
Time since most recent TBI (days)	Median (IQR) = 1 (0, 13)	Median (IQR) = 1 (0, 13)	Median (IQR) = 1 (0, 8)
Alcohol/benzodiazepine withdrawal	2 Active, 25 ruled out, 4 unclear	2 Active, 14 ruled out, 3 unclear	11 Ruled out, 1 unclear

Note: Recommended medications = medications recommended for an-needed and/or preventative use, TBI severity = defined based on VA/DOD guidelines.[25]
Abbreviations: IQR, interquartile range; LOA, length of stay; *SD*, standard deviation.

TABLE 3 Medication groups and percentage of patients started and discharged on each medication group

Medication group	Percentage of patients who were started on it	Percentage of patients who were discharged on it
Non-Recommended	**21/31 = 68%**	**7/31 = 23%**
As-needed management		
Benzodiazepines (except Midazolam)	17/31 = 55%	6/31 = 19%
Typical antipsychotics	14/31 = 45%	2/31 = 6%
Recommended	**19/31 = 61%**	**10/31 = 32%**
As-needed management		
Atypical antipsychotics[a]	19/31 = 61%	10/31 = 32%
Scheduled management		
All combined	**7/31 = 23%**	**3/31 = 10%**
Valproic acid—DVV	6/31 = 19%	4/31 = 13%
Carbamazepine	0/31 = 0%	0/31 = 0%
Amantadine	3/31 = 10%	2/31 = 6%
Beta blockers	1/31 = 3%	0/31 = 0%
Methylphenidate	1/31 = 3%	1/31 = 3%

[a]Recommended as practical alternative(s) based on limited evidence.

(71%) and White (97%). Median length of stay was 10.99 (IQR = 4.89, 26.12) and 77% of the patients included in this study, were admitted within 20 days of their latest TBI while only 13% presented more than a year after their TBI. Patients who received recommended medications, were more likely to be male (79% vs. 58%), and have moderate–severe TBI (74% vs. 42%). These differences were clinically significant although analytical statistical tests were not performed as they were not included in the study's original protocol.

Table 3 summarizes the percentage of patients who were started on each medication group during the course of admission. As depicted in this table, ~68% of patients were ordered to receive the non-recommended medication groups (benzodiazepines and typical antipsychotics) and 23% of patients were subsequently discharged on these medications. Considering atypical antipsychotics as practical alternatives for as-needed management of acute agitation in TBI, 61% of patients were started on this medication group and 32% of patients were discharged on them. Lastly, only 23% of patients were ordered to receive preventative medications and 10% of patients continued these medications at discharge. Please note that each patient could have received more than one group of medications during the course of admission.

Figure 1 depicts the percentage of patients who received recommended medications, non-recommended medications and/or atypical antipsychotics during their inpatient treatment. This graph includes both patients who were started on each medication group, as well as those who were on these medications prior to admission and continued to receive them during their hospitalization. As depicted in this graph, the majority of the patients (84%) received non-recommended medications either alone or in a combination with other medications.

Table 4 compares and contrasts ordered medications before and after psychiatric consultation. As shown in this table, the percentage of patient-days with orders to receive benzodiazepines significantly increased following psychiatric consultation ($p = 0.0001$) and the percentage of patient-days with orders to receive typical antipsychotics significantly decreased following psychiatric consultation ($p = 0.0056$). There was not a statistically significant difference between the percentage of days recommended medications were ordered before and after psychiatric consultation ($p \approx 1$). Active alcohol/benzodiazepine withdrawal occurred at a frequency of 6%,

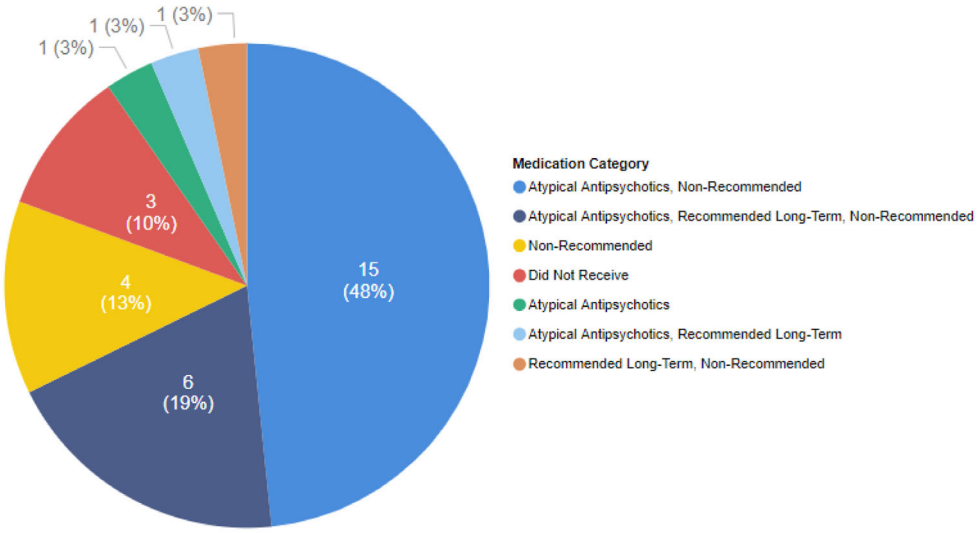

FIGURE 1 Percentage of patients who received each group of psycho-pharmacological agents. Non-recommended = Patients who received benzodiazepines OR typical antipsychotics. Recommended = Patients who received amantadine OR beta blockers (propranolol and pindolol) OR methylphenidate OR valproic acid OR carbamazepine. Atypical antipsychotics = Patients who received atypical antipsychotics that can be considered an acceptable alternative for management of acute agitation in TBI based on available evidence. Multiple medication groups = Patients who received all mentioned medication groups. Did not receive = Patients who did not receive any of the medications of interest.

TABLE 4 Number of patient-days each medication group was ordered before and after psychiatric consultation

Medication group	Number of patient-days this medication was ordered	Number of patient-days this medication was ordered before psych consult	Number of patient-days this medication was ordered after psych consult	*p* value
Non-Recommended	**215/591 = 36%**	**63/222 = 28%**	**152/369 = 41%**	**0.0023**
As-needed management				
Benzodiazepines (except Midazolam)	182/591 = 31%	47/222 = 21%	135/369 = 37%	0.0001
Typical antipsychotics	58/591 = 10%	32/222 = 14%	26/369 = 7%	0.0056
Recommended	**212/591 = 36%**	**83/222 = 37%**	**129/369 = 35%**	**0.6118**
As-needed management				
Atypical antipsychotics[a]	200/591 = 34%	78/222 = 35%	122/369 = 33%	0.6701
Scheduled management				
All combined	**102/591 = 17%**	**37/222 = 17%**	**65/369 = 18%**	**0.8547**
Valproic acid	83/591 = 14%	27/222 = 12%	56/369 = 15%	0.3686
Carbamazepine	0/591 = 0%	0/222 = 0%	0/369 = 0%	1
Amantadine	31/591 = 5%	15/222 = 7%	16/369 = 4%	0.2767
Beta blockers	15/591 = 3%	8/222 = 4%	7/369 = 2%	0.3137
Methylphenidate	4/591 = 1%	0/222 = 0%	4/369 = 1%	1

[a]Recommended as practical alternative(s) based on limited evidence.

was ruled out for 81% of the population and was unclear for the remaining 13% of patients. Benzodiazepines can be considered appropriate/necessary for the treatment of patients with alcohol/benzodiazepine withdrawal. As a result, the analysis of patient-days with orders to receive benzodiazepines before and after psychiatric consultation was repeated after excluding patients with active or unclear alcohol/benzodiazepine withdrawal. The increases in percentage of patient-days with a benzodiazepine order following psychiatric consultation remained statistically significant ($p < 0.0001$).

The most commonly prescribed benzodiazepine was lorazepam, and the most commonly prescribed atypical antipsychotic was haloperidol. The average dose of lorazepam administered per day of admission for patients who received this medication was 1.05 mg/day

and the average dose of haloperidol administered per day of admission for patients who received this medication was 2.96 mg/day. There was not a statistically significant difference in length of stay between patients who received recommended medications and those who did not receive recommended medications [Median (interquartile range): 17.07 (7.09–26.77) vs. 7.93 (3.37–17.50), respectively, $p = 0.1492$]. Among seven patients who were started on preventative recommended medications, the frequency of days of agitation was not statistically different before versus after starting preventative recommended medications (33% agitated days before vs. 34% agitated days after starting recommended medications, $p = 0.999$).

4 | DISCUSSION

In our study, benzodiazepines and/or typical antipsychotics were ordered for more than two-thirds of the patients with TBI during the course of admission. Approximately a quarter of the patients were discharged from the hospital on a benzodiazepine and/or a typical antipsychotic. Meanwhile, less than a quarter of the patients were started on medications supported by current evidence for scheduled preventative use. Our data also demonstrate a decrease in the number of days typical antipsychotics were ordered after psychiatric consultation and an increase in the number of days benzodiazepines were ordered after psychiatric consultation. This study did not detect a statistical difference in length of stay between patients who were ordered to receive recommended medications and those who were not ordered to receive them. The frequency of agitated days was not statistically different before vs. after starting recommended preventative medications.

Our results are consistent with other observational studies suggesting that antipsychotics and benzodiazepines are often used for management of agitation in the context of TBI,[22–24] especially by non-experts.[23–24] These findings are in contrast with the current lack of evidence for, and the existence of evidence against, the use of benzodiazepines and typical antipsychotics for management of agitation in TBI. Preclinical[17–20] and clinical[28–30] studies have suggested that benzodiazepines and antipsychotics may be harmful for patients with TBI as they can interfere with neurocognitive recovery, increase length of stay, and increase the duration of post-traumatic amnesia. However, there are instances in which benzodiazepines are indicated for agitation. For instance, in cases of agitation due to alcohol or benzodiazepine withdrawal, administering benzodiazepines may be necessary to prevent withdrawal seizures and/or delirium tremens. However, in our sample, the increase in the percentage of patient-days with an order to receive benzodiazepines remained statistically significant after excluding patients with active or unclear alcohol/benzodiazepine withdrawal. It is unclear whether psychiatry recommended an increase in the use of benzodiazepines for patients or whether other factors led to this increase. This finding and the interactions between psychiatrists and primary providers that could have contributed to this increase will need to be further studied.

One of the secondary objectives of this study was to detect any potential benefit in length of stay or frequency of agitated days for patients who received the recommended medications. No statistically significant difference was detected between length of stay in patients who received the recommended medications and those who did not. Having said that, potential improvements in length of stay may have been masked by differences in confounding demographic characteristics. For instance, patients who received recommended medications were more likely to be male and have moderate to severe TBI. These differences could have led to higher frequency/severity of agitation or other complications of TBI that might have prolonged length of stay. Moreover, as depicted in Figure 1, many patients who received recommended medications also received non-recommended medications that might have hindered their recovery. The frequency of agitated days was also not statistically different before versus after starting recommended scheduled medications. It is noteworthy, however, that only a small group of patients were started on these medications during admission. This small sample size might have been insufficient to detect improvement. Moreover, this retrospective chart review was not able to use standardized measures to detect slight changes in agitation. Further prospective studies with larger sample sizes and the use of standardized scales may be required to replicate the effects of these medications.

The strengths of our study include a detailed chart review of pharmacological management of agitation and/or aggression in patients with TBI incorporating a comparison of practice patterns before and after psychiatric consult and medications prescribed upon discharge. The limitations of our study include a small sample size and reliance on a retrospective review of medical records which may be subject to human error and missing information. Data extraction was not performed in duplicates which further exposes the data to human error. The classification of medication groups in this study is based on the currently available evidence and this classification may change with the advent of more robust evidence. The researchers' literature review and design of this study were performed prior to the popularity of alpha 2 agonists for the treatment of agitated delirium.[31,32] As a result, researchers did not collect information on this group of medications which is another limitation of this study.

It is also important to highlight that most of our sample were White males. In general, men account for approximately two-thirds of TBI-related medical encounters[1] which is consistent with our sample. This study's patient population was also predominantly White (97%) which is consistent with southwest Virginia's population demographics (93% White[33]). However, Carilion Clinic also serves several other regions of Virginia (Valley, Southside and Central) and several neighbouring states with lower percentages of White people. As a result, the possibility of underutilization of psychiatric consultation for management of agitation for non-White patients may need to be considered. Regardless of the reason, the demographic characteristics of our sample, limit the generalizability of the findings to non-Caucasian populations.

5 | WHAT IS NEW AND CONCLUSION

This study demonstrates the widespread use of typical antipsychotics and benzodiazepines in management of agitation in the context of TBI

and a significant reduction in the use of typical antipsychotics following psychiatric consultation. These findings suggest that educating providers about the management of agitation in TBI and further multidisciplinary collaboration may improve the care of patients with TBI.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Carilion Clinic. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available with the permission of Carilion Clinic.

PATIENT CONSENT STATEMENT

This research is a retrospective observational study. Direct patient consent was not obtained. This study was approved by Carilion Clinic's Institutional Review Board (IRB).

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