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Psychotropic Medication Use during Inpatient Rehabilitation for Traumatic Brain Injury

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Abstract

Objective—To describe psychotropic medication administration patterns during inpatient rehabilitation for traumatic brain injury (TBI) and their relationship to patient pre-injury and injury characteristics.

Design—Prospective observational cohort.

Setting—multiple acute inpatient rehabilitation units or hospitals.

Participants—2,130 individuals with TBI (complicated mild, moderate, or severe) admitted for inpatient rehabilitation.

Interventions—NA

Main Outcome Measure(s)—NA

Results—Most frequently administered was narcotic analgesics (72% of sample) followed by antidepressants (67%), anticonvulsants (47%), antianxiolytics (33%), hypnotics (30%), stimulants (28%), antipsychotics (25%), antiparkinson agents (25%), and miscellaneous psychotropics (18%). The psychotropic agents studied were administered to 95% of the sample with 8.5%

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receiving only 1 and 31.8% receiving 6 or more. Degree of psychotropic medication administration varied widely between sites. Univariate analyses indicated younger patients were more likely to receive anxiolytics, antidepressants, antiparkinson agents, stimulants, antipsychotics, and narcotic analgesics, while those older were more likely to receive anticonvulsants and miscellaneous psychotropics. Men were more likely to receive antipsychotics. All medication classes were less likely administered to Asians, and more likely to those with more severe functional impairment. Use of anticonvulsants was associated with having seizures at some point during acute care or rehabilitation stays. Narcotic analgesics were more likely for those with history of drug abuse, history of anxiety and depression (premorbid or during acute care), and severe pain during rehabilitation. Psychotropic medication administration increased rather than decreased during the course of inpatient rehabilitation in each of the medication categories except for narcotics. This observation was also true for medication administration within admission functional levels (defined by cognitive Functional Independence Measure (FIM) scores), except for those with higher admission cognitive FIM scores.

Conclusion(s)—Many psychotropic medications are used during inpatient rehabilitation. In general, lower admission FIM Cognitive groups were administered more of the medications under investigation, compared to those with higher cognitive function at admission. Considerable site variation existed regarding medications administered. The current investigation provides baseline data for future studies of effectiveness.

Keywords

Brain injuries; Rehabilitation; Antipsychotic agents; Antidepressive agents; Central nervous system stimulants; Amantadine; Polypharmacy; Physician's practice patterns; Drug therapy; Medication therapy management; Patient care

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Individuals with traumatic brain injury (TBI) frequently present to acute inpatient rehabilitation facilities with pain, hypoarousal, sleep dysregulation, behavioral dysregulation, spasticity, confusion, slowed cognitive processing, impaired memory, and affective disorders prompting prescription of multiple psychotropic medications.[1] Some of these medications are aimed at controlling behaviors to prevent harm and allow safer and more effective management of the patient (e.g. use of stimulants, benzodiazepine and antipsychotic agents to control agitation). Other medication uses are aimed at preventing comorbidities (such as seizures), and some are aimed at enhancing function (such as sleep medications, stimulants, and antiparkinson agents).[2]

Upon admission and throughout the rehabilitation stay, the rehabilitation physician typically reviews prescribed medications to continually reassess the patient's needs. This includes discontinuing medications that no longer appear necessary or may cause an adverse response, while adding other agents as deemed necessary. There is sparse literature to guide such clinical decision-making, and there are no medications that are currently approved by the United States Food and Drug Administration for the treatment of TBI. Additionally, the small body of published research is commonly limited by scientific rigor, such as lack of controlled trials, non-blinded prescribers, lack of information regarding injury, limited information on relevant data (such as severity of injury and time of injury to treatment), mixed brain injury samples, and small sample size. Evidence of medication benefit and

safety is usually extrapolated from therapeutic trials targeting common post-TBI conditions that also occur in other patient populations. An example would be the use of antipsychotic agents studied in patient populations other than brain injury and settings other than acute inpatient rehabilitation. There is a small but growing literature regarding which pharmacologic agents may be helpful in the acute rehabilitation setting for persons who sustain TBI. For example, a randomized, placebo-controlled trial of 184 TBI rehabilitation patients in vegetative state or minimally conscious state showed that amantadine was more effective than placebo in accelerating the rate of functional recovery.[3]

Various agents commonly used to manage the effects of TBI may cause adverse effects on health, function, and treatment efficiency.[4-10] For example, a retrospective review of 182 consecutive patients with moderate-to-severe TBI revealed commonly prescribed neuroleptics were associated with 7 days longer of post-traumatic amnesia (PTA).[1] In a study of individuals with TBI undergoing residential treatment, polypharmacy and use of anticholinergic medications were associated with an increased risk of falls.[11]

The degree to which psychotropic medications are used early after TBI during the course of inpatient rehabilitation is unknown. Use of psychotropic medications late after TBI was evaluated in a retrospective cohort study of 306 moderate-to-severe TBI survivors who had all been discharged from a TBI rehabilitation unit and were tracked up to 24 years post-injury. This study found that at follow-up, 58.9% were currently prescribed at least 1 medication. On average, persons with TBI were prescribed 2.64 (SD = 2.14) medications with a range of 1-12. The most prescribed medication types were anticonvulsants (25.8%), followed by antidepressants (8.2%), analgesics (8.2%) and anxiolytics (5.9%). [12]

Due to a lack of evidence on medication effects in TBI patients, medication management during acute rehabilitation is driven largely by a patient's clinical presentation and physician subjective experience or preferences. Consequently, highly variable prescribing practices exist.[2,13] There is significant need to study physicians' medication administration patterns during acute TBI rehabilitation. Medication pattern data could then be used as the basis for future research. Specifically, such data could help identify commonly used types of medicine that would benefit from effectiveness analyses, inform research design (including sample size determination), and identify the degree to which sociodemographics, injury severity, and other potential confounds (such as time from injury to rehabilitation, medical co-morbidities, function, insomnia, agitation) would need to be addressed.

The TBI Practice-Based Evidence (TBI-PBE) project provides a unique opportunity to describe patterns of psychotropic medication administration at specialized inpatient brain injury rehabilitation units in the United States and Canada including: 1) the medication agents prescribed; 2) if they were prescribed as needed (PRN) or scheduled; and 3) timing of medication initiation and discontinuation across the course of rehabilitation. The TBI-PBE data also allows evaluation of the relationship between medication prescription and patient demographic, injury, medical, and function.

Methods

Study design, study sites, and participants

The TBI-PBE Project is a 5-year, multi-center investigation of the TBI inpatient rehabilitation process.[14] 2,130 patients who received acute inpatient rehabilitation were enrolled in the project and used for the current study. The project sites included10 inpatient rehabilitation facilities: 9 in the United States and 1 in Canada. The study was approved by the local institutional review board at each study site. Inclusion criteria included: participant age of at least 14 years, informed consent from participant or their parent/guardian, and admission to the facility's brain injury unit for initial rehabilitation following TBI.

Variables and Data Collection

Collection and classification of Medications—Medication data were collected either through manual chart abstraction or electronic data download, depending on the site and availability and dependability of electronic data. Only those medications actually administered were recorded. Medications ordered but not given for any reason were not recorded. As customary during inpatient rehabilitation, medications were administered and recorded by nursing staff. Also per routine practice, a rehabilitation physician wrote the admission medication orders within minutes to hours of the patient's arrival to the inpatient rehabilitation unit and performed history and physical examination within 24 hours.

Common drug classification schemes vary, based on factors such as the chemical type of the active ingredient (e.g. “benzodiazepines”), presumed mechanisms of action (e.g. “serotonin re-uptake inhibitor”), or clinical indications for use (e.g. “antidepressant”). Medications were grouped primarily by common clinical usage/purpose and then by general mechanism of action. We also were aware that many drugs could be classified into more than 1 class (e.g. divalproex sodium as an anticonvulsant and as a mood stabilizer). For the purpose of this study, medications were classified in only 1 category. The classification scheme is outlined in Table 1. Patients may have been administered medications from multiple classes or more than 1 agent within a class, simultaneously or successively.

The medications studied included: anxiolytic agents, anticonvulsants, antidepressants, antiparkinson agents, stimulants, antipsychotics, hypnotics, miscellaneous psychotropics, and narcotic analgesics. These agents were selected among the many medications due to the need to focus the study, commonality of use in acute brain injury care, and the agent's use specifically for their central-acting property. Other psychotropic agents exist that were not studied, such as some centrally-acting antihypertensives, gastrointestinal agents, and others.

Descriptive variables—The variables for this study were chosen by the study investigators and clinicians at the onset of the project based on their clinical impressions and literature review of factors relevant to brain injury care and outcome. These data were obtained through medical record abstraction and interview with the study participants and their close others (proxy). Variables were chosen to represent patient characteristics prior to injury, post-injury before admission to rehabilitation, and during inpatient rehabilitation.

Premorbid variables studied for association with medication use included age (both continuous and categorical), gender, race, history of psychosis/schizophrenia/bipolar disorder, and history of alcohol or drug abuse.

Patient injury and medical data were abstracted from patient medical records by trained data collectors. Several variables were used to describe injury severity, including post-resuscitation Glasgow Coma Scale score in the Emergency Department, duration of PTA, and time from injury to rehabilitation admission. Any mention of presence of depression or anxiety in the medical record during acute care or at rehabilitation admission was recorded representing problems in this area premorbidly or during acute care. The extent and severity of medical illness during the rehabilitation stay was captured using the maximum Comprehensive Severity Index (CSI®) score. The CSI is derived by scoring the extent of deviation from normal physiological status for each medical complication and comorbidity present, with a higher CSI score denoting greater medical severity.[15] A brain injury CSI subscore was used to establish the severity of central nervous system illness, while a non-brain injury CSI subscore established severity of illness of all other injuries, existing chronic disorders, complications, and comorbidities. The CSI score used for this study represented the maximum CSI score for the entire course of rehabilitation.[14] Functional status and need for assistance were measured at rehabilitation admission by the Functional Independence Measure (FIM®). The FIM Cognitive and Motor scale scores were Rasch-transformed to a ratio scale using 0-100 scores.[14,16]

Rehabilitation variables included: presence of seizures at any point up to rehabilitation discharge (premorbid, during acute care, or during rehabilitation), percent of rehabilitation days with fewer than 5 hours of sleep between the hours of 9 PM and 6 AM, percent of rehabilitation stay agitated (defined as 6 shifts with Agitated Behavior Scale scores >21 out of twelve 4-hour shifts),[17] and average level of effort over the stay for physical therapy, occupational therapy, and speech therapy, combined.[18] Severity of pain was operationalized as percent of the rehabilitation stay with a patient-reported pain score of 7 or higher (out of a possible score of 10, which was the worst pain).[19]

Data processing and analysis

Description of medication administration during course of rehabilitation— Percentages were used to portray the frequency of psychotropic medication administration for each pharmaceutical class during rehabilitation.

Comparison by cognitive function at rehabilitation admission—Five relatively homogenous subgroups were created based on admission FIM Cognitive scores to stratify the impact of patients' cognitive impairments on outcomes and facilitate between group comparisons of medications administered.[14] The admission FIM Cognitive categories used were: <6, 7-10, 11-15, 16-20, >21.

Factors related to medications administered—Data were analyzed to determine patient characteristics that may differentiate whether medications in each pharmaceutical class were either administered or not administered. Medication administration patterns were also compared across treatment sites (details in the Results section under subheading of

medication administration across sites). Categorical variables with more than 2 categories (e.g. site, age, race/ethnicity) were evaluated using the chi-square test; categorical variables with 2 categories (e.g. gender) were evaluated with Fisher's exact test. Continuous variables (e.g. brain injury and non-brain injury CSI) were evaluated using the independent-samples t-test. To minimize Type I error, only differences reaching an alpha level of $p<.001$ were considered significant. Correction for multiple comparisons was not performed due to the exploratory nature of this descriptive paper.

Calculation of rehabilitation weeks—In order to study the timing of medication initiation and discontinuation across the course of rehabilitation we depicted medication administration by week of stay in rehabilitation. All patients with a rehabilitation length of stay (RLOS) of 8 days or less were considered to have only 1 admission week. All others have an admission (week 1) and a discharge week, at a minimum. Patients with RLOS of 9-15 days have 2 weeks; RLOS of 16 and 17 have 3 weeks (with the admission week comprised of only 6 days). All patients with an RLOS ≥18 days have the following: 18-22 have 3 weeks; 23-29 have 4 weeks; 30-36 have 5 weeks; etc. There are no weeks shorter than 4 days, and none longer than 8. For RLOS with remainders of 1 when divided by 7 (e.g. 22, 29, etc.) the extra day is added to the discharge week to create an 8-day week.

Results

Study Sample

Our sample of 2,130 patients with TBI was 73% male, 74% white, 37% married, and 51% employed at the time of injury. Average age of the sample was 45 years. Cause of injury was most commonly vehicular accidents (56%), followed by falls or flying objects (32%), violence (7%), and sports (2%). Mean RLOS was 27 days (SD = 20). The mean Rasch-transformed FIM Motor score at admission was 33 (SD = 19) and mean Rasch-transformed FIM Cognitive score was 37 (SD = 20). The mean time from injury to rehabilitation admission was 29 days (SD = 34). The first article in this series[14] further summarizes the demographic and injury characteristics for the sample.

Patterns of Medication Administration

Medication use by admission FIM cognitive categories—Medication use is summarized by admission FIM Cognitive subgroup in tables 2 and 3, based on time-variant factors. For all medication classes except anticonvulsants, use was less frequent among those in the highest FIM Cognitive subgroup than in the lower groups. Conversely, medication use was greater for those with worse cognitive function at the time of rehabilitation admission. Use was higher in the 2 lower FIM Cognitive groups than middle and higher functioning subgroups for antiparkinson agents, stimulants, and anxiolytics, while antipsychotic and miscellaneous psychotropics had the opposite pattern. In general, as admission FIM Cognitive groups increased in function, antidepressant use was less. For example, antiparkinson agents were used for 35% and 26% of the patients in the 2 lowest FIM Cognitive subgroups, with frequency decreasing with higher admission cognitive function. Anticonvulsant use was higher for the 2 highest FIM cognitive groups, although use did not substantially vary across the 5 subgroups.

The most commonly prescribed agents were narcotic analgesics (72% of the sample), followed in decreasing frequency by antidepressants (67%), anticonvulsants (47%), antianxiety agents (33%), hypnotics (30%), stimulants (28%), antiparkinson agents (25%), antipsychotics (25%), and miscellaneous psychotropics (18%). Expanded detail on the frequency of specific medications at the level of general mechanism within each pharmaceutical class by admission FIM Cognitive category, is available in tables A and B in the supplemental digital content.

Anxiolytic agents—The percentage of patients administered anxiolytic medication remained roughly the same from admission to discharge for the overall sample and for all FIM Cognitive subgroups. Only 19% received an anxiolytic during the first 2 days and 19% during the last 2 days, with 33% receiving this class at some point during the stay. The primary anxiolytics prescribed were benzodiazepines, with 29% of patients receiving them at some point during the rehabilitation stay—approximately half of individuals receiving it on a regular basis, and half on an “as needed” basis. Lorazepam was the most common benzodiazepine prescribed, accounting for 68% of the benzodiazepine-based anxiolytics administered, followed by clonazepam (12%), and alprazolam (10%). H1 receptor antagonists (i.e., hydroxyzine) were rarely utilized, and were prescribed PRN more often than scheduled. Of the entire sample, 7% of patients received buspirone, which was predominately prescribed on a scheduled basis, with usage increasing over the RLOS.

Anticonvulsant agents—Nearly half (47%) of patients received an anticonvulsant at some point during their rehabilitation stay, with 35% receiving 1 during the first 2 days, 39% the last 2 days, and 28% during both intervals. The most commonly used anticonvulsants were the calcium channel and sodium channel antagonists. The most common calcium channel antagonist used was levetiracetam (61% of agents in this class administered to 21% of the sample); the most common sodium channel antagonists used were valproic acid (39% of agents in this class), phenytoin (37%), and carbamazepine (9%).

Antidepressant agents—Two thirds of the patients (67%) received an antidepressant at some point during their rehabilitation stay, 44% during the first 2 days, 55% the last 2 days, and 37% during both intervals. The most commonly used antidepressants were serotonin antagonist and reuptake inhibitor (SARI; i.e., trazodone) and selective serotonin reuptake inhibitors (SSRIs; i.e., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), while only a minority of patients received tricyclic antidepressants (TCAs; i.e., desipramine, nortriptyline, amitriptyline, and doxepin), norepinephrine-dopamine reuptake inhibitor (NDRI; i.e., bupropion), noradrenergic and specific serotonergic antidepressant (NaSSA; i.e., mirtazapine), and serotonin and norepinephrine reuptake inhibitors (SNRIs; i.e., duloxetine, venlafaxine, and milnacipran). Antidepressants were generally prescribed as scheduled with only occasional PRN use, with the exception of SARI (i.e. trazodone), which was used in both manners, consistent the common practice of prescribing this agent for insomnia.

Antiparkinson agents—Antiparkinson agents were administered to only 25% of the patients at some point during rehabilitation, with use substantially increasing over the stay,

from 11% receiving this class of medication during the first 2 days to 20% the last 2 days. The most commonly used antiparkinson was an NMDA antagonist (i.e., amantadine) administered to 17% of the sample, followed by dopamine agonist (i.e., bromocriptine, pramipexole, ropinirole). These agents were generally administered on a scheduled basis with rare PRN use. Bromocriptine accounted for 95% of the dopamine agonists administered.

Stimulant agents—Stimulants were administered to only 28% of the sample. Similar to the antiparkinson and miscellaneous therapeutic agents, stimulants were predominately started after admission. Use of stimulants increased over the course of the stay, and these agents were commonly used among those with long RLOS. Patterns of administration appear consistent within the various agents contained in the stimulant class. The most commonly used were the norepinephrine-dopamine-5HT agonists (i.e., agents containing amphetamine, dextroamphetamine, or methylphenidate) that were used by 23% of the sample. Less commonly used were armodafinil/modafinil and the norepinephrine agonist atomoxetine. The stimulant agents were generally used on a scheduled basis.

Antipsychotic agents—Antipsychotic agents were received by a quarter of the sample at some point during their stay. The overall percentage of use did not increase during the stay, with 16% receiving it the first 2 days and 15% the last 2 days, and 10% receiving during both intervals. Second generation antipsychotics were administered more frequently (24% of the sample) than first generation ones (3%). Second generation medications were most commonly received as scheduled but were also used PRN. On the other hand, first generation antipsychotics were more often administered PRN than scheduled. Those with longer RLOS had slightly higher usage. Of the second generation antipsychotics administered, quetiapine accounted for 48%, followed by risperidone (19%), olanzapine (15%), and ziprasidone (14%).

Hypnotic agents—Hypnotic agents were administered to 30% of the sample. Use increased slightly from admission to later in the stay and was particularly common for those with longer RLOS. Most commonly prescribed in this class were non-benzodiazepine GABA-A agonists [i.e., zolpidem (88% of the class), eszopiclone (11%), zaleplon (<1%)], followed by occasional (5%) use of benzodiazepine GABA-A agonists [i.e., temazepam (62% of the class), midazolam (38%)] and 3% use of other hypnotics (i.e., chloral hydrate, propofol, phenobarbital). Melatonin agonists were rarely used. In general, hypnotics were slightly more likely to be used PRN than scheduled.

Miscellaneous Psychotropic agents—Miscellaneous psychotropics were used relatively less often than other agents, with 18% of patients receiving 1 of these agents at some point during their rehabilitation stay. They were most commonly initiated later in the stay and more frequently administered to those with longer RLOS. The most commonly prescribed in this class were acetylcholinesterase inhibitors (AChE-I; i.e., donepezil, physostigmine, rivastigmine) at 9% and “other” (i.e., glatiramer acetate, interferon beta 1a, nicotine, varenicline) at 9%. The AChE-I were generally prescribed after rehabilitation admission and later in the stay. Use was greatest in the later weeks of the rehabilitation stay

and for those with longer RLOS. On the other hand, administration of the "other" psychotherapeutics was greatest during the first 2 days of rehabilitation with decreased use over the remaining stay. For those with longer RLOS, these agents were used less over time. These findings are largely accounted for by the prescription of nicotine or nicotine patch, which accounted for 98% of the use in the "other" category. This class of medications was most commonly administered as scheduled with occasional PRN use. The AChE-I were used PRN for 17% of the patients receiving this agent.

Narcotic Analgesics—The majority of patients received narcotics during their rehabilitation stay (72% overall) with a high use across FIM categories, even among those with lower levels of function. Most of the use occurred at admission (55% of sample during the first 2 days of rehabilitation) with decreased use occurring over the rehabilitation stay—45% of the sample received narcotic analgesics during last 2 days of rehabilitation. Narcotics were consumed for an average of 16 days, accounting for a mean 65% of the RLOS administered. Narcotics were received as both scheduled and PRN. PRN administration was used as commonly in the lower functioning group who are expected to have impaired communication as in the higher functioning groups. Scheduled use occurred across functional groups with less scheduled narcotic administration in the highest functioning group.

Relation of Patient Factors and Medication Administration

Table 4 shows the relationship between receiving a medication from a psychotropic pharmaceutical class at any time during rehabilitation and *pre-injury characteristics and injury related variables*. Age was highly associated with receiving most medications, the exception being hypnotics. In general, younger patients were more likely to receive anxiolytics, antidepressants, antiparkinson, stimulants, antipsychotics, and narcotic analgesics. In contrast, older patients were more likely to receive anticonvulsants and miscellaneous psychotropics. Males were more likely to receive antipsychotics. History of psychosis, bipolar disorder, or schizophrenia was also associated with being more likely to receive an antipsychotic, but was unrelated to receiving other classes of medications. Anxiolytics, antidepressants, and hypnotics were less likely to be used in minority populations. Anxiolytics, anticonvulsants, antidepressants, and narcotic analgesics were more likely to be used when there was a history of depression or anxiety (premorbid history or during acute care). Anti-depressants, anti-psychotics, and psychotropics were more likely to be used when a patient had a prior history of substance abuse.

In contrast to table 4, table 5 shows the relationship between having ever been administered a medication and patient characteristics *during the rehabilitation stay*. Multiple indices of more severe impairment (percent of stay agitated, effort given in therapies, severity of brain impairment, severity of non-brain comorbidities, and length of PTA) were related to increased drug administration in nearly all categories. Other indices indicative of greater difficulties during rehabilitation (i.e., percent of days in pain and percent of days with less than 5 hours sleep) were related to increased medication administration with the exceptions of anti-psychotics and psychotropics. Having seizures during rehabilitation increased the likelihood of administration of anticonvulsants as well as narcotic analgesics.

Psychotropic medication exposure summary and concurrent use—Table 6 depicts the percentage of patients receiving specific quantities of psychotropic medications during rehabilitation, overall, and by admission cognitive category. Only 5.0% of the patients were never administered psychotropic medications during their rehabilitation stay, while 8.5% were prescribed only 1 of the psychotropic medications; 31.8% were prescribed 6 or more of these agents at some point during their stay. These results could occur if all 6 were prescribed simultaneously, or sequentially (1 after the other) while the physician was searching for an effective drug. More likely, some were given at the same time, with some dropping off and others being added. During the first 2 days of rehabilitation 5.5% of patients were on at least 6 psychotropic medications, while 13.5% were on at least 6 of these medications during the last 2 rehabilitation days. In general, those in the lower admission FIM Cognitive categories received a greater number of psychotropic medications studied (3-8 agents) than those in higher FIM Cognitive categories, in which most received 0-5 agents.

Medication administration across sites—Medication administration patterns varied greatly across treatment sites as summarized in table 7. Sites with high antipsychotic use had lower use of anxiolytics, and vice versa. Sites with high antiparkinson administration had less antipsychotic use, and vice versa. For anticonvulsant use, most sites were similar except 1 site where 80% of their patients received an anticonvulsant agent during their rehabilitation stay. With a range of 7-31%, miscellaneous psychotropic agents were used relatively infrequently at some sites. Antidepressant use was uncommon at 1 site (27%), with use ranging 46-91% across the others. The site with the highest use of antidepressants had a practice pattern of using the antidepressants SARI and tertiary amine TCAs as their first line treatment of insomnia. Across sites, antiparkinson agent use ranged 1% - 57% and stimulants use 5-50%.

Discussion

This large sample, multicenter study documents the extent to which psychotropic medications are administered to treat patients with TBI during inpatient rehabilitation. In 9 broad categories of medications, the percent of overall use varied from 18 to 72% with a mean of 42% (table 2: % ever received), and 31.8% were exposed to at least 6 of the psychotropic agents studied during rehabilitation (table 6). These results suggest 1) a strong "culture of intervention"[20] with the prevalent use of unproven medications to advance recovery in this group of facilities that specialize in brain injury management; 2) an urgent need to control patient behavior; and/or 3) a strong desire to stimulate recovery. We found considerable variation across sites. Marked variation in clinical practice is likely a reflection of the relative lack of high quality research available in neuropharmacology post TBI. With the absence of solid data, clinicians may base their treatment decisions on information gleaned from accepted treatments for other impairment groups with similar problems to treat issues such as agitation, headache, pain, insomnia, and sleep disorder. In the absence of better evidence, the prescriber is often reliant on their subjective clinical impressions, expert opinion, and a multitude of case studies and open-label case series reinforced by and overlying natural recovery.

In this study, univariate analyses indicated potential differences related to age and race in the percentage of patients prescribed varying classes of medications. The extent to which younger patients may be more likely to be administered anxiolytics, antidepressants, antiparkinson/stimulants, antipsychotics, and narcotic analgesics requires further analysis that controls for injury severity and secondary conditions. Further testing for nonlinear relationships between age and medication administration (i.e., both very young and very old patients being less likely to be prescribed medications) is also warranted.[21] Anxiolytics, antidepressants, antipsychotics, hypnotics, and antiparkinson agents were less likely to be used with ethnic minorities, particularly those of Asian and Hispanic descent. Given the relatively small number of Asian and Hispanic patients in this sample, further investigation is warranted to evaluate the extent that injury severity and secondary conditions versus unmeasured factors (such as differential cultural preferences or site differences in ethnicity and prescribing preferences) are related to medication use.

This study did not capture information about the primary symptom(s) that physicians targeted for each medication prescribed. Tables 4 and 5 indirectly provide insight into the potential variability in symptoms associated with the pharmaceutical classes of medication administered. For example, 29% of those who received anxiolytics did not have anxiety mentioned in their medical record (as having been present premorbidly, during acute care, or at the time of rehabilitation admission), suggesting that many may be treated with this class of medication for other reasons such as agitation or insomnia. Similarly, 61% of those who received antidepressants did not have mention of depression present premorbidly or during acute care, suggesting that pain, sleep disorders, and/or behavior are being treated by commonly prescribed medications that were classified as antidepressants. For example, the SARI trazodone is often used in this population for sleep induction. Similar findings were observed for antipsychotics (24% lacked mention of premorbid history of psychosis, bipolar disorder, or schizophrenia). Of those administered anticonvulsants, 41% did not have a seizure during acute care or rehabilitation indicating use for seizure prophylaxis or other reasons (such as behavior control or pain management). The broad range of medication applications highlights the importance of patient education and communication with co-treating physicians regarding the targeted use of medications prescribed at the time of discharge from rehabilitation and after.

Our univariate analyses found statistically significant center effects across pharmaceutical classes. Given the wide variability between centers with regard to age, time from injury to rehabilitation admission, injury etiology and severity, and levels of functional impairment,[22] further analyses are required to determine the extent that center effects exist independent of other confounds. With the limited literature on neuropharmacology effectiveness post TBI to guide treatment decisions, practice variation at least between physicians would not be surprising.[23,24]

Antiparkinson and stimulant administration was low in comparison to the authors' expectations and in comparison to other psychotropic medications (narcotic analgesics, antidepressants, anticonvulsants, antianxiolytics, and hypnotics). Antiparkinson agents were administered to 25% of patients at some point during rehabilitation (most commonly amantadine and bromocriptine). In clinical practice, these medications are often used in the

treatment of several rehabilitation relevant issues including: poor arousal, agitation, disinhibition, lack of initiation, akinetic mutism, and cognitive impairment. Similarly, stimulant administration (28% of sample received) was surprisingly low given that symptoms of inattention, lack of initiation, poor arousal, and slow processing speed are cardinal features of moderate and severe TBI. Stimulants were administered predominately to those with lower admission FIM Cognitive scores. The most commonly used stimulants were methylphenidate, modafanil, and atomoxetine. Considering the greater use of other classes (such as antidepressants, anticonvulsants, antianxiolytics, hypnotics), perhaps antiparkinson and stimulant agents could have a greater role in the management of the TBI patient (such as the agitated, confused, difficult to manage, or slow to recover patient) [25-30] than is currently being used by some physicians. In studies of subacute TBI, patients receiving methylphenidates have shown short-term improvements in attention, concentration, motor memory, cognitive processing speed, and overall function. [26,27] Scientific evidence suggests amantadine may help minimize the impact of many deficits commonly following TBI, particularly disordered consciousness, cognitive impairments, and behavioral dysregulation.[3, 29-31]

Conversely, prescription of narcotics was surprisingly high, despite the risk of their cognitive sedating properties. Narcotic use is very high across all functional cognitive levels, with nearly 75% of all patients receiving these medications at least once during their stay. While narcotics were overwhelmingly prescribed on a PRN basis, the median percent of days that patients were administered these medications suggests that in practice they were fairly regularly used. Applying these findings clinically, the clinician is advised to use caution with administering pain medication and consider incorporation of objective measures of function as well as pain into the assessment and ongoing administration.

Antipsychotic agents were received by 25% of the sample at some point during their stay. It is common for practitioners to use this class of medication to assist with controlling agitation post TBI. This particular use is somewhat controversial as the blocking of dopamine is not always considered to be productive in terms of recovery.[1,4] However, second generation antipsychotics have less D2 dopamine receptor effect, and are thought to be preferable over first generation agents; though they still have a considerable side effect profile. Second generation antipsychotics have been proposed by some in the field as preferred treatment for agitation and psychosis due to TBI.[32,33] Quetiapine accounted for 48% of the second generation antipsychotics administered, followed by risperdone (19%), olanzapine (15%), and ziprasidone (14%).

Future Research Directions

The use of this multi-center, longitudinal data to evaluate the effectiveness of medication treatments in real-world clinical settings offers both opportunities and challenges. Findings from this initial investigation of medication administration patterns during TBI inpatient rehabilitation provides valuable data that can inform the research design of future medication comparative effectiveness studies. Ninety percent of the patients in our study were administered 2 or more psychotropic medications during their stay, with 60% administered between 3 and 7. Because of the administration of multiple medications at the

same time or within the short time frame of rehabilitation, future research requires that study designs carefully evaluate the effects of psychotropic medications alone and in combination on the primary outcomes of interest. Future research will also need to take into account dosing levels and duration of treatment, while controlling for participant-specific effects. Mixed effects quantile stratification propensity adjustment strategies for longitudinal analyses may be suited for such treatment effectiveness analyses.[34,35] Based on our findings, participant effects that should be considered for stratified propensity adjustment for each primary outcome include age, timing of administration, history of Axis I mental health disorders, severity of cognitive impairment, and pain. The potential confounding effects of center and race should be further evaluated to determine whether these are true effects or are encapsulated within the covariates already listed for potential stratification adjustment. Evaluation, and where necessary, adjustment of individual covariates for nonlinear relationships and outlier effects is essential given the frequent observance of large SDs.

Study Limitations

The findings of this study represent the patterns of administration at highly specialized brain injury rehabilitation centers and may not represent the patterns of use at all rehabilitation units. In particular, this study may be unique in regards to the medical complexity and neurologic functional level of the patients, training and experience of the clinicians, academic environment, resources of the facilities, and demographics of the study sample (primarily Caucasian). The acute care hospital medical records were not consistently available, thus we did not include medications used during acute care. The study focused on key agents commonly used to improve arousal, behavior, function, and control central nervous system issues associated with TBI. The study was limited to 9 medications categories. There are several psychotropic medications that were not examined here, but were administered, such as alpha agonist and beta-blocking antihypertensive agents, metoclopramide, proton pump inhibitors, and a host of agents with anticholinergic effects.

The targeted goals for medication prescription are not known in this study. Medications designed and approved for 1 use are commonly used for other purposes. For instance, antidepressants may be useful for correction of sleep disorders, pain, and anxiety as well as depression. Anxiolytics may be used for sleep and behavior modification as well as anxiety. Anticonvulsants are commonly used for neuropathic pain and mood stabilization as well as seizure prevention or management. Antipsychotics may be administered for insomnia, anxiety, psychosis, and agitation. The present study reveals the type of psychotropic agents used but not the purpose. Data about severity of injury, duration of PTA, agitation, pain, seizures, sleep, and cognition were assessed for association with administration of these agents, and thereby, provide some information on use. However, caution should be used in presuming the use of the medications in this study.

Conclusion

Many psychotropic medications are used during inpatient rehabilitation. A wide variety of applications are perceived for each class of psychotropic medications and individual agents within classes. Knowledge of prescribing patterns may inform further research such as

comparative effectiveness studies. In general, lower admission FIM Cognitive groups were administered more of the medications under investigation, compared to those with higher cognitive function at admission. Considerable site variation existed regarding medications administered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AChE-I	Acetylcholinesterase inhibitors
APAP	Acetaminophen
COMT	Catechol-*O*-methyltransferase
CSI	Comprehensive Severity Index
FIM	Functional Independence Measure
GABA-A	Gaba-aminobutyric acid-A
MAO	Monoamine oxidase
NaSSAs	Noradrenergic and specific serotonergic antidepressants
NDRI	Norepinephrine-dopamine reuptake inhibitor
NMDA	N-Methyl-D-aspartate
PRN	Pro re nata (as needed)
PBE	Practice-based evidence
PTA	Posttraumatic amnesia

RLOS	Rehabilitation length of stay
SARI	Serotonin antagonist and reuptake inhibitors
SNRI	Serotonin and norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitor
TBI	Traumatic brain injury
TCA	Tricyclic antidepressant

Table 1
Classification for the Psychoactive Medications Administered

Major Drug Class & General Mechanism	Pharmacologic Agents Received # (%)*	Total # Patients Receiving Agent†
Anxiolytic		
Gaba-aminobutyric acid-A (GABA-A) agonist	lorazepam (478; 68%), clonazepam (85; 12%), alprazolam (67; 10%), diazepam (66; 9%), chlordiazepoxide (5; <1%)	701
H-1 receptor antagonist	hydroxyzine (21; 100%)	21
Other	buspirone (151; 100%)	151
Anticonvulsant		
Calcium channel antagonist	levetiracetam (440; 61%), gabapentin (219; 30%), pregabalin (65; 9%)	724
GABA-A agonist	tiagabine (4; 100%)	4
Sodium channel antagonist	valproic acid (239; 39%), phenytoin (229; 37%), carbamazepine (56; 9%), topiramate (38; 6%), lamotrigine (23; 4%), oxycarbamazepine (13; 2%), fosphenytoin (12; 2%) primidone (3; <1%), zonisamide (2; <1%)	612
Other	lacosamide (3; 100%)	3
Antidepressant		
Norepinephrine-Dopamine reuptake inhibitor (NDRI)	bupropion (30; 100%)	30
(NaSSA)	mirtazapine (70; 100%)	70
Serotonin antagonist and reuptake inhibitor (SARI)	trazodone (1124; 100%)	1124
Serotonin and norepinephrine reuptake inhibitor (SNRI)	duloxetine (54; 52%), venlafaxine (45; 44%), milnacipran (4; 4%)	103
Selective serotonin reuptake inhibitor (SSRI)	paroxetine (44; 8%), fluoxetine (37; 6%)	81
Tricyclic Antidepressant (TCA) - secondary amine	nortriptyline (34; 92%), desipramine (3; 8%)	37
TCA - tertiary amine	amitriptyline (62; 95%), doxepin (3; 5%)	65
Antiparkinson		
Catechol-*O* -methyltransferase (COMT) inhibitor	entacapone (1; 100%)	1
Dopamine agonist	bromocriptine (190; 95%), pramipexole (7; 3%), ropinirole (4; 2%)	201
Monoamine oxidase (MAO) inhibitor	benzatropine (15; 79%), rasagiline (2; 11%), selegiline (2; 11%)	19
N-Methyl-D-aspartate (NMDA) antagonist	amantadine (361; 100%)	361
Other	carbidopa + levodopa (28; 88%), levodopa (4; 13%)	32
Stimulant		
Norepinephrine agonist	atomoxetine (56; 100%)	56
Norepinephrine -Dopamine-5HT agonist	sulfate + dextroamphetamine saccharate + dextroamphetamine sulfate (24; 5%), amphetamine + dextroamphetamine (6; 1%), dextroamphetamine (3; <1%)	490
Other	modafinil (117; 96%), armodafinil (6; 4%)	123
Antipsychotic		
First generation / Typical	11%)	55

Major Drug Class & General Mechanism	Pharmacologic Agents Received # (%)*	Total # Patients Receiving Agent†
Second generation / Atypical	quetiapine (307; 48%), risperidone (119; 19%), olanzapine (93; 15%), ziprasidone (92; 14%), aripiprazole (25; 4%), paliperidone (1; <1%)	637
Hypnotic		
Benzodiazepine GABA-A agonist	temazepam (63; 62%), midazolam (38; 38%)	101
Non-benzodiazepine GABA-A agonist	zolpidem (482; 88%), eszopiclone (62; 11%), zaleplon (3; <1%)	547
Melatonin agonist	ramelton (13; 100%)	13
Other	chloral hydrate (36; 57%), propofol (26; 41%), phenobarbital (1; 2%)	63
Narcotic Analgesic		
Narcotic	oxycodone (864; 37%), acetaminophen (APAP) + hydrocodone (688; 30%), morphine (205; 9%), fentanyl (145; 6%), tramadol (142; 6%), hydromorphone (85; 4%), propoxyphene N + APAP (84; 4%), codeine (48; 2%), methadone (44; 2%), APAP + codeine (14; <1%), meperidine (4; <1%), buprenorphine (4; <1%), propoxyphene N (4; <1%)	2234†
Miscellaneous Psychotropic		
Acetylcholinesterase inhibitor (AChE-I)	donepezil (178; 95%), rivastigmine (6; 3%), physostigmine salicylate (3; 2%)	187
NMDA antagonist	memantine (29; 100%)	29
Other	nicotine (204; 98%), interferon beta 1a (2;<1%), glatiramer acetate (1; <1%), varenicline (1; <1)	208

*#patients who received agent among sample of 2130 with medication data; % of patients who received the agent among the other agents in that mechanism within that classification

†Patients may receive more than one agent within a mechanism

Table 2

Summary information on psychoactive medications administered during rehabilitation, by pharmaceutical categoryand level of functional cognition

Pharmaceutical category	FIM Cognitive score at admission	N*	% ever rec'd†	% rec'd† first 2 days	% rec'd† last 2 days	% rec'd† first & last 2 days	% rec'd† 5+ days	mean # days (for those rec'd†)	median # days (for those rec'd†)	mean % stay (for those rec'd†)	median % stay (for those rec'd†)	% days PRN	% days Sched‡	% days Unknown PRN/ Sched‡
Anxiolytic	Overall	2130	33	19	19	11	23	17	12	56	58	37	53	10
	Adm cog <=6	339	48	24	26	14	31	21	18	50	50	40	45	14
	Adm cog 7-10	374	44	23	26	12	32	19	14	53	52	37	55	7
	Adm cog 11-15	495	31	18	18	11	22	17	13	60	67	36	57	7
	Adm cog 16-20	408	28	20	17	13	20	13	9	62	73	33	56	11
	Adm cog >=21	504	20	13	12	7	14	12	10	60	65	39	50	11
Anticonvulsant	Overall	2130	47	35	39	28	43	23	17	81	100	6	76	19
	Adm cog <=6	339	50	32	40	25	48	35	28	76	93	8	71	21
	Adm cog 7-10	374	52	34	42	26	48	27	23	77	94	3	85	12
	Adm cog 11-15	495	46	34	39	28	44	22	18	83	100	4	80	16
	Adm cog 16-20	408	46	38	41	33	43	19	15	87	100	4	73	22
	Adm cog >=21	504	41	37	32	28	36	13	12	83	100	10	67	24
Antidepressant	Overall	2130	67	44	55	37	61	23	18	78	93	27	60	13
	Adm cog <=6	339	77	47	64	40	73	34	29	79	94	23	62	15
	Adm cog 7-10	374	76	48	63	39	72	26	22	78	90	25	65	10
	Adm cog 11-15	495	66	46	54	38	60	21	19	80	95	30	57	13
	Adm cog 16-20	408	69	49	58	42	62	17	14	78	95	28	57	15
	Adm cog >=21	504	53	35	41	28	42	15	12	74	90	30	57	13
Antiparkinson	Overall	2130	25	11	20	8	23	25	21	73	83	3	83	14
	Adm cog <=6	339	53	24	40	17	49	30	26	70	79	4	84	12
	Adm cog 7-10	374	40	18	31	13	36	25	22	71	85	1	87	12
	Adm cog 11-15	495	21	8	19	7	20	24	19	78	86	2	82	15
	Adm cog 16-20	408	15	4	12	4	13	16	14	71	75	5	72	23

Pharmaceutical category	FIM Cognitive score at admission	N*	% ever rec'd†	% rec'd† first 2 days	% rec'd† last 2 days	% rec'd† first & last 2 days	% rec'd† 5+ days	mean # days (for those rec'd†)	median # days (for those rec'd†)	mean % stay (for those rec'd†)	median % stay (for those rec'd†)	% days PRN	% days Sched‡	% days Unknown PRN/ Sched
	Adm cog >=21	504	6	4	6	3	5	14	14	80	100	5	73	23
Antipsychotic	Overall	2130	25	16	15	10	21	20	15	65	75	23	62	15
	Adm cog <=6	339	38	18	23	10	34	27	20	57	55	29	49	22
	Adm cog 7-10	374	34	21	23	13	30	21	17	66	78	24	61	15
	Adm cog 11-15	495	28	21	18	13	23	18	15	71	89	18	74	8
	Adm cog 16-20	408	22	16	11	7	18	15	13	63	75	17	71	12
	Adm cog >=21	504	10	8	6	5	7	12	9	65	70	33	50	16
Hypnotic	Overall	2130	30	14	20	10	23	18	13	60	67	48	42	10
	Adm cog <=6	339	36	14	23	9	29	24	21	57	58	34	51	16
	Adm cog 7-10	374	37	17	26	12	31	22	18	62	70	41	50	9
	Adm cog 11-15	495	31	15	20	10	25	18	14	61	68	47	46	7
	Adm cog 16-20	408	25	13	16	8	16	11	9	57	64	55	35	9
	Adm cog >=21	504	24	13	16	9	17	11	8	62	70	68	23	10
Narcotic analgesic	Overall	2130	72	55	45	36	59	16	13	65	77	63	26	11
	Adm cog <=6	339	71	50	35	26	59	21	17	56	51	63	25	12
	Adm cog 7-10	374	74	50	40	29	60	18	14	57	59	61	30	9
	Adm cog 11-15	495	73	56	42	35	59	16	13	62	70	64	26	10
	Adm cog 16-20	408	75	60	51	43	60	14	12	69	90	57	32	12
	Adm cog >=21	504	69	59	52	46	58	14	11	78	100	69	19	12
Miscellaneous Psychotropic	Overall	2130	18	8	15	6	16	19	15	69	75	9	78	13
	Adm cog <=6	339	24	4	22	3	23	26	21	58	59	16	76	8
	Adm cog 7-10	374	19	7	14	5	17	21	17	65	68	10	77	13
	Adm cog 11-15	495	21	10	17	8	20	17	16	73	81	4	84	12
	Adm cog 16-20	408	19	12	16	9	17	16	14	75	90	5	78	17
	Adm cog >=21	504	10	7	7	6	8	13	9	72	98	14	69	18
Stimulant	Overall	2130	28	7	22	6	26	23	18	66	72	5	83	12

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Pharmaceutical category	FIM Cognitive score at admission	N*	% ever rec'd†	% rec'd† first 2 days	% rec'd† last 2 days	% rec'd† first & last 2 days	% rec'd† 5+ days	mean # days (for those rec'd†)	median # days (for those rec'd†)	mean % stay (for those rec'd†)	median % stay (for those rec'd†)	% days PRN	% days Sched‡	% days Unknown PRN/ Sched
	Adm cog <=6	339	57	16	41	12	54	29	27	67	75	4	79	17
	Adm cog 7-10	374	44	10	36	9	43	25	22	68	78	3	89	8
	Adm cog 11-15	495	25	5	20	4	23	19	16	63	64	5	84	11
	Adm cog 16-20	408	15	5	12	4	13	13	11	65	67	9	78	14
	Adm cog >=21	504	8	2	7	2	6	11	9	64	64	10	79	10

*10 patients were excluded due to missing Admission FIM cognitive score

†r'cd = received

‡sched = scheduled

Table 3

Sample size by week and percent with psychoactive medication administration by pharmaceutical class, week of rehabilitation, and level of cognitive function at admission

Pharmaceutical class	FIM Cognitive score at admission	% rec'd week 1	% rec'd week 2	% rec'd week 3	% rec'd week 4	% rec'd week 5	% rec'd week 6	% rec'd week 7	% rec'd week 8	% rec'd week 9
Sample size by week*	**Overall**	2130	2008	1551	1065	707	482	339	215	153
	Adm cog <=6	339	333	323	288	223	160	107	79	59
	Adm cog 7-10	374	371	337	266	185	121	90	56	34
	Adm cog 11-15	495	482	387	236	127	73	48	30	27
	Adm cog 16-20	408	381	253	126	74	50	42	24	17
	Adm cog >=21	504	432	242	140	91	71	47	23	16
Anxiolytic	Overall	24	22	23	23	26	28	30	32	31
	Adm cog <=6	31	30	29	30	30	29	30	33	27
	Adm cog 7-10	30	27	27	26	30	35	40	41	38
	Adm cog 11-15	24	23	21	20	24	29	29	30	37
	Adm cog 16-20	23	19	19	19	19	20	24	21	29
	Adm cog >=21	16	14	14	13	14	15	15	22	19
Anticonvulsant	Overall	39	39	39	41	42	43	42	46	48
	Adm cog <=6	37	38	38	42	41	45	43	49	59
	Adm cog 7-10	39	39	41	45	52	52	51	52	53
	Adm cog 11-15	38	40	41	43	46	48	46	50	52
	Adm cog 16-20	41	41	40	41	49	44	40	29	24
	Adm cog >=21	39	34	31	23	12	13	13	22	19
Antidepressant	Overall	56	59	62	65	66	67	66	67	69
	Adm cog <=6	59	65	65	68	71	72	71	63	73
	Adm cog 7-10	61	65	69	68	71	72	74	70	62
	Adm cog 11-15	58	59	62	67	61	63	65	73	78
	Adm cog 16-20	60	63	64	64	68	60	52	63	59
	Adm cog >=21	44	47	47	48	51	54	53	65	63
Antiparkinson	Overall	16	21	25	29	32	32	32	31	27

Pharmaceutical class	FIM Cognitive score at admission	% rec'd week 1	% rec'd week 2	% rec'd week 3	% rec'd week 4	% rec'd week 5	% rec'd week 6	% rec'd week 7	% rec'd week 8	% rec'd week 9
	Adm cog <=6	35	41	41	44	44	45	45	42	36
	Adm cog 7-10	26	29	32	35	38	42	43	39	32
	Adm cog 11-15	15	19	22	25	28	30	25	27	30
	Adm cog 16-20	9	14	15	18	18	12	14	13	12
	Adm cog >=21	4	6	7	6	4	3	0	0	0
Antipsychotic	Overall	20	19	19	20	21	22	23	24	29
	Adm cog <=6	25	24	24	27	27	30	33	35	42
	Adm cog 7-10	26	25	23	23	23	25	27	27	29
	Adm cog 11-15	24	21	20	21	19	15	17	17	26
	Adm cog 16-20	19	19	19	15	16	18	17	8	6
	Adm cog >=21	9	7	8	7	7	7	6	4	6
Hypnotic	Overall	21	22	24	26	26	26	25	25	27
	Adm cog <=6	21	24	23	26	26	25	22	25	25
	Adm cog 7-10	25	26	29	32	30	34	33	34	38
	Adm cog 11-15	23	23	26	31	32	36	35	33	33
	Adm cog 16-20	18	18	19	18	18	12	10	0	6
	Adm cog >=21	20	18	18	16	14	14	15	13	19
Narcotic analgesic	Overall	65	60	55	49	49	45	40	42	40
	Adm cog <=6	59	56	52	47	46	45	41	42	41
	Adm cog 7-10	63	59	52	47	50	48	44	48	38
	Adm cog 11-15	67	60	55	51	50	52	46	47	48
	Adm cog 16-20	69	63	58	52	54	36	31	25	29
	Adm cog >=21	66	62	59	48	42	37	30	35	38
Miscellaneous Psychotropic	Overall	11	13	15	14	16	18	19	20	18
	Adm cog <=6	6	10	15	19	20	23	27	28	25
	Adm cog 7-10	11	13	13	13	16	18	14	20	15
	Adm cog 11-15	14	16	18	16	16	15	23	23	19
	Adm cog 16-20	15	18	18	14	14	14	12	13	12
	Adm cog >=21	8	8	7	6	7	10	9	4	0

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Pharmaceutical class	FIM Cognitive score at admission	% rec'd week 1	% rec'd week 2	% rec'd week 3	% rec'd week 4	% rec'd week 5	% rec'd week 6	% rec'd week 7	% rec'd week 8	% rec'd week 9
Stimulant	Overall	15	21	27	33	38	39	38	35	34
	Adm cog <=6	30	42	46	51	56	57	57	52	49
	Adm cog 7-10	25	33	38	43	44	51	49	45	38
	Adm cog 11-15	13	18	21	28	33	34	35	30	37
	Adm cog 16-20	9	13	13	11	14	6	5	0	0
	Adm cog >=21	4	6	7	7	5	4	4	0	0

*10 patients were excluded due to missing Admission FIM cognitive score

†r'cd = received

Table 4

Bivariate Associations of Patient Pre-injury and Injury Characteristics with Ever Receiving Medication During Rehabilitation

Variable	Anxiolytic		Anti-Convulsant		Anti-Depressant		Anti-Parkinson		Anti-Psychotic		Hypnotic		Narcotic-Analgesic		Miscellaneous Psychotropic		Stimulant	
	% or Mean(SD)*	p-value	% or Mean(SD)*	p- value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p- value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value
Age (continuous)	42(19); -3†	<.001	47(22); 5†	<.001	44(20); -3†	0.008	42(20); -3†	0.004	41(19); -4†	<.001	44(20); -1†	0.526	42(20); -8†	<.001	47(20); 4†	0.001	40(20); -6†	<.001
Age (category)		<.001		<.001		<.001		0.009		<.001		0.018		<.001		<.001		<.001
<30 years	32%	.	41%	.	67%	.	26%	.	27%	.	28%	.	76%	.	13%	.	33%	.
≥30-<45 years	40%	.	44%	.	75%	.	30%	.	32%	.	35%	.	82%	.	22%	.	30%	.
≥ 45-<65 years	37%	.	50%	.	69%	.	25%	.	26%	.	31%	.	74%	.	21%	.	25%	.
≥ 65-<75 years	26%	.	57%	.	59%	.	21%	.	17%	.	31%	.	61%	.	16%	.	20%	.
≥75-<85 years	19%	.	58%	.	61%	.	16%	.	20%	.	28%	.	53%	.	23%	.	19%	.
≥85 years	15%	.	44%	.	46%	.	18%	.	6%	.	17%	.	39%	.	17%	.	14%	.
Gender		0.959		0.408		0.235		0.082		<.001		0.314		0.516		0.077		0.481
Female	33%	.	48%	.	65%	.	22%	.	20%	.	28%	.	73%	.	16%	.	26%	.
Male	33%	.	46%	.	68%	.	26%	.	28%	.	31%	.	72%	.	19%	.	28%	.
Race/Ethnicity		<.001		0.011		<.001		0.014		0.004		<.001		0.01		0.003		0.015
Asian/Other/Unknown	19%	.	30%	.	47%	.	18%	.	19%	.	17%	.	58%	.	9%	.	16%	.
Black	27%	.	49%	.	58%	.	31%	.	23%	.	24%	.	71%	.	14%	.	27%	.
White Non-hispanic	35%	.	47%	.	71%	.	24%	.	27%	.	32%	.	74%	.	20%	.	29%	.
White Hispanic	24%	.	47%	.	60%	.	19%	.	15%	.	23%	.	70%	.	15%	.	21%	.
History of drug abuse		0.001		0.957		<.001		0.664		<.001		0.178		<.001		<.001		0.51
No	31%	.	47%	.	65%	.	25%	.	23%	.	29%	.	70%	.	16%	.	28%	.
Yes	39%	.	47%	.	74%	.	26%	.	35%	.	32%	.	81%	.	27%	.	26%	.
History of alcohol abuse		0.06		0.526		<.001		0.075		<.001		0.03		0.511		<.001		0.649
No	31%	.	47%	.	64%	.	26%	.	21%	.	31%	.	72%	.	14%	.	28%	.
Yes	35%	.	46%	.	72%	.	23%	.	33%	.	27%	.	73%	.	26%	.	27%	.
History of psychosis/bipolar disorder/ schizophrenia		0.049		0.05		0.908		0.9		<.001		0.556		0.185		0.091		<.001
No	32%	.	46%	.	67%	.	25%	.	24%	.	30%	.	72%	.	18%	.	28%	.

Variable	Anxiolytic		Anti-Convulsant		Anti-Depressant		Anti-Parkinson		Anti-Psychotic		Hypnotic		Narcotic-Analgesic		Miscellaneous Psychotropic		Stimulant	
	% or Mean(SD)*	p-value	% or Mean(SD)*	p- value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p- value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value
Yes	43%	.	57%	.	66%	.	24%	.	55%	.	33%	.	79%	.	25%	.	12%	.
Depression prior to or during acute care		<.001		<.001		<.001		0.441		0.002		<.001		<.001		0.385		0.11
No	30%	.	44%	.	61%	.	24%	.	24%	.	27%	.	70%	.	17%	.	27%	.
Yes	39%	.	53%	.	82%	.	26%	.	30%	.	36%	.	79%	.	19%	.	30%	.
Anxiety prior to or during acute care		<.001		<.001		<.001		0.448		<.001		0.064		<.001		0.355		0.502
No	29%	.	45%	.	64%	.	25%	.	24%	.	29%	.	69%	.	18%	.	28%	.
Yes	50%	.	55%	.	80%	.	23%	.	33%	.	34%	.	86%	.	19%	.	26%	.
Post-resuscitation Glasgow Coma Scale score		<.001		<.001		<.001		<.001		0.036		0.003		<.001		0.238		<.001
Intubated/Sedated	41%	.	47%	.	78%	.	31%	.	29%	.	39%	.	79%	.	22%	.	36%	.
Mild (13-15)	29%	.	46%	.	65%	.	14%	.	21%	.	26%	.	76%	.	18%	.	15%	.
Moderate (9-12)	27%	.	33%	.	64%	.	17%	.	24%	.	28%	.	76%	.	13%	.	24%	.
Severe (3-8)	36%	.	40%	.	71%	.	31%	.	29%	.	31%	.	73%	.	17%	.	36%	.
Missing	29%	.	57%	.	60%	.	23%	.	23%	.	28%	.	67%	.	18%	.	23%	.

*%=percent of patients with that characteristic who received the specified medication class; mean (SD) = mean (SD) for those patients with that characteristic who received the specified medication class

†The difference between those who received the specified medication class and those who did not receive the specified medication class.

A negative value indicates that the characteristic is less common for those who received the medication class as opposed to those who did not recieve the medication class (e.g. -3 for age indicates patients who received anxiolytics were on average 3 years younger than those who did not).

Table 5

Bivariate Associations of Rehabilitation Characteristics with Ever Receiving Medication During Rehabilitation

Variable	Anxiolytic		Anti-Convulsant		Anti-Depressant		Anti-Parkinson		Anti-Psychotic		Hypnotic		Narcotic-Analgesic		Miscellaneous Psychotropic		Stimulant	
	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value
Seizure any time up to rehabilitation discharge		0.023		<.001		0.153		0.621		0.208		0.463		<.001		0.011		0.785
No seizure	32%	.	41%	.	68%	.	25%	.	26%	.	30%	.	74%	.	17%	.	28%	.
Yes, 1 or more seizure	38%	.	80%	.	63%	.	26%	.	23%	.	28%	.	64%	.	23%	.	28%	.
Days from injury to rehabilitation admission	35(42); 8†	<.001	28(32); -3†	0.036	31(37); 7†	<.001	37(40); 10†	<.001	29(32); 0†	0.998	31(30); 2†	0.159	28(33); -6†	0.001	29(33); -0†	0.937	37(43); 10†	<.001
Admission FIM cognitive category		<.001		0.031		<.001		<.001		<.001		<.001		0.204		<.001		<.001
Score <=6	48%	.	50%	.	77%	.	53%	.	38%	.	36%	.	71%	.	24%	.	57%	.
Score 7-10	44%	.	52%	.	76%	.	40%	.	34%	.	37%	.	74%	.	19%	.	44%	.
Score 11-15	31%	.	46%	.	66%	.	21%	.	28%	.	31%	.	73%	.	21%	.	25%	.
Score 16-20	28%	.	46%	.	69%	.	15%	.	22%	.	25%	.	75%	.	19%	.	15%	.
Score >=21	20%	.	41%	.	53%	.	6%	.	10%	.	24%	.	69%	.	10%	.	8%	.
Admission FIM motor category		<.001		0.167		<.001		<.001		<.001		<.001		<.001		0.604		<.001
Score <22.05	44%	.	50%	.	77%	.	43%	.	29%	.	37%	.	77%	.	19%	.	45%	.
Score 22.05-28.75	30%	.	46%	.	58%	.	21%	.	30%	.	28%	.	72%	.	16%	.	27%	.
Score 28.75-40.65	31%	.	46%	.	70%	.	16%	.	25%	.	27%	.	77%	.	19%	.	18%	.
Score 40.65-44.25	23%	.	46%	.	67%	.	12%	.	23%	.	26%	.	79%	.	14%	.	14%	.
Score 44.25-53.36	24%	.	46%	.	66%	.	14%	.	26%	.	27%	.	68%	.	17%	.	16%	.
Score >53.36	21%	.	41%	.	51%	.	9%	.	17%	.	23%	.	59%	.	17%	.	14%	.
Percent of days with <5 hours sleep	36(23); 8†	<.001	33(23); 3†	<.001	32(22); 2†	0.079	34(22); 5†	<.001	33(22); 3†	0.005	36(23); 8†	<.001	33(23); 7†	<.001	31(23); 0†	0.936	31(20); -0†	0.942
Average Therapy Level of Effort	4(1); -0.4†	<.001	4(1); -0.2†	<.001	4(1); -0.3†	<.001	4(1); -0.8†	<.001	4(1); -0.4†	<.001	4(1); -0.2†	<.001	4(1); 0.0†	0.618	4(1); -0.3†	<.001	4(1); -0.6†	<.001
Maximum CSI brain injury component	59(25); 16†	<.001	50(25); 4†	<.001	52(25); 12†	<.001	67(23); 24†	<.001	58(22); 13†	<.001	55(25); 10†	<.001	50(25); 5†	<.001	55(24); 8†	<.001	66(23); 25†	<.001
Maximum CSI non-brain injury component	30(24); 7†	<.001	26(22); 3†	<.001	27(21); 6†	<.001	30(23); 6†	<.001	30(23); 7†	<.001	30(23); 7†	<.001	27(22); 9†	<.001	24(19); -1†	0.578	28(21); 5†	<.001
Posttraumatic amnesia duration (days)	49(54); 18†	<.001	40(46); 4†	0.045	42(47); 14†	<.001	61(54); 32†	<.001	45(47); 10†	<.001	44(45); 9†	<.001	37(42); -2†	0.324	43(44); 7†	0.006	60(54); 31†	<.001

Variable	Anxiolytic		Anti-Convulsant		Anti-Depressant		Anti-Parkinson		Anti-Psychotic		Hypnotic		Narcotic-Analgesic		Miscellaneous Psychotropic		Stimulant	
	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value	% or Mean(SD)*	p-value
Time of posttraumatic amnesia clearing		<.001		0.151		<.001		<.001		<.001		<.001		0.007		<.001		<.001
Cleared PTA prior to rehab admission	26%	.	47%	.	64%	.	11%	.	17%	.	28%	.	78%	.	14%	.	12%	.
Cleared PTA on rehab admission day	14%	.	40%	.	44%	.	12%	.	9%	.	9%	.	88%	.	14%	.	9%	.
Cleared PTA after rehab admission day	39%	.	50%	.	72%	.	36%	.	32%	.	33%	.	73%	.	21%	.	40%	.
Percent of days with pain score 7+	20(26); 4†	<.001	20(27); 5†	<.001	19(26); 7†	<.001	12(20); -7†	<.001	18(24); 1†	0.528	19(26); 3†	0.007	23(27); 20†	<.001	19(27); 2†	0.117	11(18); -8†	<.001
Percent of rehabilitation stay agitated	16(25); 10†	<.001	11(22); 5†	<.001	11(21); 5†	<.001	13(22); 5†	<.001	20(27); 15†	<.001	13(24); 6†	<.001	9(20); 2†	0.04	14(24); 6†	<.001	13(23); 6†	<.001

*%=percent of patients with that characteristic who received the specified medication class; mean (SD) = mean (SD) for those patients with that characteristic who received the specified medication class

†The difference between those who received the specified medication class and those who did not receive the specified medication class.

A negative value indicates that the characteristic is less common for those who received the medication class as opposed to those who did not recieve the medication class (e.g. 8 for days injury to rehab admission indicates that patient who received anxiolytics had on average 8 days longer days from injury to rehab admission than those who did not).

Table 6

Percent of patients who received psychoactive medications during rehabilitaiton by number received and admission cogntitive functional level

	Overall			Adm FIM Cog ≤6			Adm FIM Cog 7-10			Adm FIM Cog 11-15			Adm FIM Cog 16-20			Adm FIM Cog ≥ 21		
# psycho active meds rec'd	% ever rec'd*	% rec'd* 1st 2 days	% rec'd* last 2 days	% ever rec'd*	% rec'd* 1st 2 days	% rec'd* last 2 days	% ever rec'd*	% rec'd* 1st 2 days	% rec'd* last 2 days	% ever rec'd*	% rec'd* 1st 2 days	% rec'd* last 2 days	% ever rec'd*	% rec'd* 1st 2 days	% rec'd* last 2 days	% ever rec'd*	% rec'd* 1st 2 days	% rec'd* last 2 days
0	5.0	13.0	12.7	2.4	13.9	7.7	2.4	11.8	9.4	4.4	11.5	14.1	4.2	9.6	10.8	10.1	17.3	18.7
1	8.5	21.9	17.3	3.2	15.6	10.3	4.5	20.6	10.7	7.5	23.0	15.2	8.6	22.1	19.9	16.3	25.6	27.4
2	12.6	23.4	17.4	5.9	24.2	15.9	7.0	21.1	14.7	10.7	21.6	16.6	15.7	25.2	19.1	20.4	25.0	19.8
3	14.6	17.5	17.0	9.7	18.0	16.2	11.2	18.2	16.8	17.4	19.4	19.0	16.2	18.6	17.6	16.3	13.9	15.5
4	14.3	12.0	13.9	10.9	14.2	16.2	12.6	11.0	17.4	15.8	14.5	14.1	17.2	10.5	14.2	14.3	10.1	9.1
5	12.9	6.6	8.4	14.7	6.2	10.6	13.9	9.6	10.4	13.5	6.1	8.5	14.2	7.4	8.1	9.5	4.4	5.2
6	10.4	3.5	6.0	11.2	5.0	11.2	15.5	5.3	7.0	13.1	1.8	7.1	8.8	3.9	3.4	4.4	2.4	2.8
7	7.3	1.4	3.8	12.4	1.8	6.8	11.0	1.3	7.2	5.5	1.4	2.2	4.7	1.7	3.7	5.0	1.0	0.8
8	4.9	0.5	1.5	8.8	0.9	2.9	7.2	0.8	2.7	4.4	0.2	0.8	3.9	0.5	1.0	2.0	0.4	0.8
9	3.5	0.1	1.1	6.5	0.3	1.2	4.5	0.3	1.6	2.2	0.0	1.6	3.7	0.2	1.0	1.6	0.0	0.0
10	2.2	0.0	0.3	4.1	0.0	0.0	4.5	0.0	1.1	1.8	0.2	0.4	1.2	0.0	0.2	0.2	0.0	0.0
>10	3.5	0.0	0.4	10.0	0.0	0.9	5.7	0.0	1.0	3.6	0.2	0.4	1.6	0.2	0.9	0.0	0.0	0.0

* r'cd = received

Table 7

Percent that Received Medication Classification by Treatment Site

Variable	Anxiolytic	Anti-Convulsant	Anti-Depressant	Anti-Parkinson	Anti-Psychotic	Hypnotic	Narcotic-Analgesic	Miscellaneous Psychotropic	Stimulant
	% patients received*	% patients received*	% patients received*	% patients received*	% patients received*	% patients received*	% patients received*	% patients received*	% patients received*
Site 1	39%	42%	52%	10%	14%	23%	77%	11%	12%
Site 2	50%†	42%	91%†	57%†	18%	49%†	87%	23%	50%†
Site 3	17%‡	44%	50%	4%	62%†	13%‡	79%	9%	40%
Site 4	20%	46%	64%	16%	13%‡	18%	78%	7%‡	5%‡
Site 5	21%	60%	64%	25%	24%	21%	58%	37%†	40%
Site 6	20%	51%	46%	11%	27%	13%‡	48%	8%	28%
Site 7	33%	52%	89%	25%	35%	29%	90%†	31%	25%
Site 8	27%	80%†	27%‡	46%	23%	31%	49%	21%	6%
Site 9	38%	47%	76%	33%	28%	44%	77%	15%	35%
Site 10	22%	22%‡	48%	1%‡	15%	15%	33%‡	12%	5%‡
Average	29%	49%	61%	23%	26%	26%	68%	17%	25%

*All p-values were <0.001 for differences across sites.

†highest percentage for medication class

‡lowest percentage for medication class