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PHARMACOLOGIC TREATMENT OF AGITATION IN TRAUMATIC BRAIN INJURIES

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Date    12/02/2018
Abstract

This case report looks at a middle aged woman with a traumatic brain injury (TBI) from a domestic assault and subsequent behavioral disturbances that required medication management. There are no current guidelines on what to use to treat agitation and aggression related to TBI’s, so a literature review was done to look at research for treatment of this situation. Neuroleptic medications were utilized with varying effectiveness; however, the literature review contraindicates this class of medication as it can delay cognitive recovery based on limited human studies. Other medications are discussed in various articles, but there are no current FDA approved medications for behavioral disturbances in patients suffering from TBI’s. Environmental modifications are noted to be the most effective method of reducing behavioral disturbances by multiple articles.

*Keywords:* traumatic brain injury, post-traumatic agitation, aggression, pharmacologic management
Pharmacologic treatment of agitation in traumatic brain injuries

Traumatic brain injuries (TBI) can be a devastating event to occur to any individual with lasting changes that can affect both the individual in question and those who are a part of their life. Part of healing from a TBI includes recovering from post-traumatic amnesia, delirium and associated complications; some of which include depression, anxiety, sleep disturbances and agitation. According to Segal (2017), three main areas that are affected by neuropsychiatric sequelae are cognition, emotions, and behaviors. According to Oyesanya, Bowers, Royer, and Turkstra (2018), major concerns of treating patients with TBI’s reported by nursing staff surveyed was worry about causing no additional harm to the patient, but also preventing harm to staff and family as violence and impulsivity can be unpredictable with this population of patients. Family members may have no idea how to manage this change in behavior from their loved one, so nursing staff and providers need to have a good idea of how to educate both patient and family regarding treatment of the aggression and impulsivity with environmental factors and pharmacological methods. When a provider is looking at interventions to help with those post-traumatic complications, they need to consider the injury the brain incurred and how medications might affect cognitive recovery.

**Background**

This literature review will look at a single case report of a patient who suffered a traumatic brain injury and had significant neuropsychiatric sequelae, including episodes of agitation to see how the patients care could have been improved or changed or if the interventions used were appropriate in the patient’s specific situation. There are many ways that a person can incur a traumatic brain injury, all of which cause lasting after effects physically and mentally and can drastically change someone’s quality of life going forward.
Depression is noted to be the most common complication from a TBI, as those affected are four times more likely to attempt suicide than the general population, usually within the first five years (Segal, 2017). There is also an increased risk of developing other mental health conditions; there is a five point three times increased risk of developing bipolar disorder, a five point eight times increased risk of post-traumatic stress disorder and/or panic disorder, and two point three times increased risk of generalized anxiety disorder. It is also noted by Segal (2017) that one-third to one-half of patients with TBI’s also are affected by personality changes including apathy, emotional lability, increased impulsivity and decreased judgement skills. These personality changes can lead to an increased risk of agitation or aggression. Add on the risk factors that indicate even further potential of aggression that include premorbid affective disorders, substance abuse, personality disorders and frontal lobe injury from the traumatizing event and it becomes apparent that agitation and aggression is something that needs to be addressed early to ensure therapeutic interventions are utilized.

**Case Report**

The patient that is presented in this case report is a fifty-year-old woman who was physically assaulted in her apartment by an unknown assailant. Per the emergency room report, neighbors had heard screaming and items being broken in the apartment and called 911 for a possible domestic abuse situation. The patient was found by EMS lying on her back with a laceration over her left eye and was only responsive to painful stimuli with slurring speech. It was noted by EMS that there were multiple broken windows, furniture and alcohol containers strewn around the apartment. The patient had a Glasgow Coma Score of ten at time of EMS intervention, and needed to be restrained on the cart as she was attempting to pull at medical equipment.
According to the patient’s mother, the patient had a history of borderline personality disorder, adjustment disorder with mixed anxiety and depressed mood, major depressive disorder with psychosis, substance abuse concerns including use of alcohol, cocaine and marijuana laced with embalming fluid and apparently had been experiencing auditory and visual hallucinations throughout her life but had not had consistent psychiatric care nor was consistent with taking medications. Previous psychiatric medication trials included citalopram, trazodone, aripiprazole, quetiapine and lithium; according to the patient’s mother, the patient did very well when on lithium.

A copy of one of the initial emergency room nurse notes is as follows:

[Female patient] presents after an assault. Struck multiple times in left forehead and side of head with unknown object. Mostly somnolent, arousable to stimuli. Arousable to physical stimuli and muttering incomprehensibly. CT head and C spine negative on prelim reads. 3 cm laceration above her left eyebrow, not repaired. Lactate 2.9, getting fluids and tetanus. Plan for sober and re-eval. (medical chart, July 29, 2018)

The patient was eventually transferred to a medical unit for further examination and stabilization as she was still somnolent and resisting examination. There was initial concern for a subarachnoid hemorrhage but that was ruled out on a repeat head CT. Labs indicated that troponins were negative, liver function tests were normal and did not indicate hepatic encephalopathy. Differential diagnoses on initial history and physical by medicine physician indicates acute metabolic toxic encephalopathy and/or TBI, victim of domestic assault, possible alcohol intoxication, hypokalemia, leukocytosis, and elevated lactate. The psychiatric consult and neurology consult teams concurred that this was most likely hypoactive delirium secondary
to trauma, TBI, polysubstance abuse and urinary tract infection (UTI). Differentials considered for altered mental status included acute stress reaction, cocaine washout, and cognitive decline secondary to TBI or toxin from marijuana laced with embalming fluid. A lumbar puncture was obtained with unremarkable results, no indication of encephalopathy noted. An MRI was attempted but unsuccessful due to patient’s agitation and behaviors. She was treated for her UTI; hypokalemia and elevated lactate were resolved during her stay on the medical unit. She continued to have cognitive deficiencies that were thought to be a possible unusual post-TBI syndrome or related to decompensated mental illness. The medical providers stated that after patient was medically stabilized she would require inpatient psychiatric care for stabilization of cognitive and behavioral challenges. She was transferred to inpatient psychiatry on August 9th, 2018 and was noted to be oppositional, hostile, uncooperative, sarcastic and irritable as well as frequently redirecting questions back to her care team instead of answering them. She had been started on risperidone 1 mg BID and olanzapine 10 mg at bedtime while on medical to help mediate the behaviors exhibited with minimal response.

A note from the registered nurse working with the patient on August 12th showed what type of difficulties the patient was having in day to day life, including how to eat and how to take care of herself generally at this time.

The [patient] was lying in bed saying "leave me alone" when the staff was attempting to get her up. This writer and staff took off the covers and assisted her to stand to sit in the wheelchair. Even though she kept saying no thank you and leave me alone she stood and then was directed and brought to the lounge where she sat in a chair. A tray was put in front of her and when staff attempted to help her set up her tray "I don't need any help leave me alone" She picked up a whole pancake with her hands and ate a bite and threw it
down. At this point the writer started to cut up the patients pancake and put margarine and syrup on it and after that she ate everything on her tray. She sat at the table and ate lunch when it was brought and drank fluids.

She keeps repeating the same things over and over about "Leave me alone" "I don't need to do anything"

A: Continue to be confused, no insight or she doesn't appears [sic] to understand how to get up and where to go and even how to put syrup and margarine on her pancakes

R: The patient would not have gotten up to eat or drink if the staff had not gotten her up despite her protests to eat and drink and she needs very basic instructions on how to get up and where to go and what to do.

P: Continue on one to one for falls, encourage to be up and eat and drink (medical chart, August 12, 2018)

Her medications were changed; risperidone and olanzapine were discontinued and haloperidol 5 mg added, which seemed to be more effective as the patient was out in the milieu more and engaging more appropriately with staff and providers. She did not appear as overtly anxious but was noted to still be very preoccupied with returning to her apartment. Upon review of the case by physical medicine and rehabilitation consultants (PM&R), they recommended against the use of dopaminergic agents, anticholinergic agents, benzodiazepines, GABA agonists and sedating agents. PM&R recommended the use of second generation antipsychotics (SGA) or mood stabilizers for treatment of aggression along with environmental adaptations. The reasoning for using those medications was because dopaminergic, anticholinergic and other contraindicated agents are thought to prevent motor and cognitive recovery in animal studies. Haloperidol was discontinued for the patient after fourteen days of use; risperidone was restarted
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and citalopram added. The provider had added clonazepam to treat the patient’s increased anxiety and agitation a week after restarting risperidone. Another fourteen days after initiation of risperidone, haloperidol was restarted and both olanzapine and risperidone discontinued, due to the significant decompensation of the patient that necessitated her to be placed in restraints and in seclusion multiple times. The benefit of restarting haloperidol was determined to be greater than the risks of delaying or reducing the patient’s motor and cognitive recovery. She did appear to be improving after restarting the haloperidol as she was less anxious, less agitated and not needing as many interventions by staff members.

Literature Review

Review of the literature included a search in CINAHL and Cochrane Library databases. There were a variety of articles addressing traumatic brain injuries, post-traumatic stress disorders, agitation and aggression but the majority of pertinent information addressed in these articles appeared to be from animal studies as there has been limited quality human studies at this time. There are also a limited number of articles written in the last eight years to use exclusively and so articles were reviewed from as far back as 2003, mostly from neurological rehabilitation, brain injury and medicine journals. There were no discovered pertinent articles found from psychiatric journals aside from studies about treating dementia related behaviors, which may be useful for future research as this patient did end up with a discharge diagnosis of moderate neurocognitive disorder in setting of TBI with behavioral disturbance.

According to the U.S. food and drug administration (FDA) website (2018) and Kalra and Watanabe (2017), there are no FDA approved medications to treat traumatic brain injuries. Medications discussed and used in the articles reviewed are all being used off-label for the subsequent behavioral symptoms occurring from traumatic brain injuries. As there have been
few studies done on medications for use in agitation or behavioral disturbances related to traumatic brain injuries, there hasn't been enough empirical evidence for the FDA to support and approve a particular medication for use in the clinical setting.

Several of the articles reviewed talked about environmental changes and nursing management as primary methods to reduce behavioral disturbances and agitation. Environmental changes would include making the environment low stimulus, having simple clock faces / large digital clocks available, pictures of loved ones, and providing a consistent schedule with the least amount of staff changes as possible. According to Mortimer and Berg (2017), patients with traumatic brain injuries have a lower threshold for stress and frequent changes, and visitors or high stimulus events can push them into becoming agitated. Mortimer and Berg (2017) conducted a literature review on agitation in patients with TBI’s, looking specifically at nursing management. The authors only briefly address the use of pharmacologic agents in treating agitation in this population, however their literature review should be considered when treating agitated patients as a lot of the same environmental factors are mentioned in multiple articles. Providers should look at other reasons why a patient may be agitated, including assessing for pain that isn’t being addressed or bowel and bladder concerns. The authors mention using music and aromatherapy as alternative methods of trying to treat agitation, but there is a need for this to be looked into further as that could become too much stimulus for some patients to handle.

Park, Williams and Lee (2016) did look into the effect of preferred music vs classical relaxation music vs no music in patients with severe TBI’s as measured by the Agitated Behavior Scale (ABS). Despite the small sample size of fourteen patients and limited time frame of exposure to the stimuli (one hour), preferred music was noted to be more apparent in decreased
ABS scores post-exposure. The researchers did state that they kept the volume of the music low as to not overwhelm the patients’ tolerance of sound, as well as limited other sources of noise. There were no relevant studies found that looked at the effect of aromatherapy on agitation from TBIs, though some studies did look at how aromatherapy may impact patients with dementia related behaviors that could be reviewed further in the future.

Eisenberg, Im, Swift and Flanagan (2009) wrote a critical review of the management of treatment of agitation. At the time of the article, there were no standards of care or guidelines for clinicians to use when treating patients with TBI’s and many providers were attempting to treat agitation in patients with modalities from the psychiatric field. This included using psychiatric medications to attempt to reduce levels of agitation and behaviors in patients. Eisenberg et al. (2009) are also adamant that the environment these patients are in should be as low stimulus and consistent as possible. The authors stated that non-pharmacological measures should always be tried first and to address any underlying factors that may be contributing to agitation such as pain or confusion. Pharmacological measures can be tricky, as many of the agents that would be used to reduce agitation and anxiety can actually prolong cognitive recovery in patients. Benzodiazepines, opiates and first generation antipsychotics (FGA) are included in those medications that are believed to worsen cognitive recovery. The authors talk about reducing the number of medications a patient may be taking to try to alleviate side effects that may be occurring, such as removing prophylactic anticonvulsant medications if possible to do so or using a medication that can act as both prophylactic anticonvulsant and as a mood stabilizer.

Antipsychotics are highly common for providers to use in acute agitation, though rat studies indicate a delayed cognitive recovery with use of FGA. This has not been observed when using second generation antipsychotics (SGA) with the exception of risperidone, which was
shown to delay cognitive recovery in rats. According to Elovic, Lansang, Li and Ricker (2003), however, risperidone was one of the most promising SGA for use in treating agitation in patients with TBI’s. That study did mention that there are limited human trials and most of the information was obtained from animal studies. The authors did also find that haloperidol and other FGA’s delayed cognitive recovery however, correlating with the findings of later studies. A feasibility study being done by Deb et al. (2018) is looking at the effectiveness of risperidone in post-traumatic agitation. The study was to be completed by October 2018, but new information about results have not been published yet. The authors were completing a double blind randomized control trial (RCT) that looked at twelve weeks of treatment with risperidone versus use of a placebo by using the MOAS scale to measure verbal and physical aggression. However, limitations of this study include having participants with premorbid psychiatric conditions excluded.

In 2014, according to Ponsford et al., an international team of researchers and clinicians called INCOG put out an article with recommendations for management of cognition following a traumatic brain injury; they had written a chapter specifically looking at post-traumatic amnesia and delirium. Part of what they also found in their research was that neuroleptic medications should be avoided as much as possible since they can slow cognitive recovery. These researchers looked at both risperidone and haloperidol use in rats and found that the rats had a significantly delayed motor recovery, spatial learning ability and slowed swim speed.

Eisenberg et al. (2009) indicates that tricyclic antidepressants (TCA) are reported to be very helpful, however selective serotonin reuptake inhibitors (SSRI) have not been quite as effective with treating agitation. Propranolol has been shown to reduce agitation in the majority of studies, though this is not shown to be effective in all studies. Neurostimulants such as
amantadine and methylphenidate are found to help improve cognition as well as agitation in patients, though these results were still from smaller studies.

Kalra and Watanabe (2017) discussed using mood stabilizers in post-traumatic agitation, but stated that there is limited evidence in treating this condition. The authors performed a prospective observational cohort study with 2,130 individuals being reviewed who have been diagnosed with a TBI. About half of those patients were treated with an anticonvulsant while in rehabilitation, but there was not strong evidence to establish a clear determination regarding effectiveness. There was significant inconsistency in the way that post-traumatic agitation was measured, which should be addressed in future studies.

A double blind RCT was done by Zhang and Wang (2017) that looked at the effectiveness of methylphenidate in treating agitation related to brain injuries. The study was thirty weeks long and had thirty-six participants which were divided in a 1:1 ratio. The study results were found to be consistent with what the authors expected, including decreased mental fatigue and improved cognitive functional recovery. There was nothing in this study that looked to see if methylphenidate had any effect on agitated behaviors with the patients. It could be hypothesized that improved cognitive function would correlate with decreased agitation and behaviors, but it has not been determined by any studies at this point.

A historic cohort study in 2004 by Harmsen, Geurts, Fasotti and Bevaart looked at sixty patient files over a five and a half-year period in a rehabilitation center to see if there were any patterns in the use of neuroleptic medications for treatment of agitation. Of the sixty patient files reviewed, twenty-eight patients had post-traumatic amnesia and sixteen had positive behavioral disturbances. Seven patients received neuroleptic medications to treat the positive behavioral disturbances, however five of those seven had significant extrapyramidal symptoms or lab
abnormalities that required the discontinuation of those medications. For many of the patients, it was noted by the authors that environmental changes and/or swapping to non-neuroleptic behavior modifying medications eliminated the need for neuroleptic medication treatment of behavioral disturbances over a period of about three weeks. Three of the drugs mentioned that seemed to have a positive impact on reducing behavioral disturbances were amantadine, mirtazapine and propranolol.

Mysiw et al. (2009) looked at the impact of acute care medications and how they effected the recovery of patients with traumatic brain injuries. What the authors had found was that if a patient had post-traumatic amnesia, there was generally a longer period of time to clear if they were also taking neuroleptic or narcotic medications. This was talked about frequently in various articles as narcotics, benzodiazepines and neuroleptics are some of the most common medications prescribed for this patient population. The authors did have findings that supported the use of stimulants such as amphetamine for increasing recovery time, as well as finding that the use of antidepressants may help improve recovery.

In the case report being looked at earlier in the paper, it appeared that the providers tried to do the right things. They had initially utilized SGA’s before going to a FGA, obtained consults from rehab providers and attempted to re-utilize smaller doses of the medications found to be safer for cognitive recovery such as olanzapine, risperidone, and citalopram. The patient was not responding to these medications well and in fact was becoming so confused and agitated that she ended up in restraints or seclusion multiple times. There were not any charted attempts to use beta-blockers or amphetamines, which could have been explored to reduce anxiety and promote cognitive recovery. Looking at the response of the medications compared to the risk of delaying cognitive recovery when it comes to patient and staff safety as well as the patient’s
quality of care is extremely important to keep in mind when it comes to developing treatment plans. Compounding the problem in this case report was that the patient ended up on an inpatient psychiatric floor, where the milieu could be loud and disruptive. This patient would have potentially been better suited for a rehabilitation unit that could have done more to utilize environmental factors to try and reduce behaviors, but she was not medically complex enough and had gotten rejected for placement at several rehabilitation facilities. She also needed a locked unit as she was disorganized and disoriented and may have tried to elope from an unlocked rehab unit or facility.

**Implications**

Looking at the information gathered from the literature review, there are many factors to keep in mind for pharmacologic treatment of agitation in patients with TBI’s. Most important is making sure to evaluate and treat any underlying issues that may be contributing to behaviors such as pain, bladder and bowel issues or other physical complaints. There is also need to ensure the environment is altered to suit the patient as well as reorient them; this is the first step to reducing behaviors before utilizing medications. If the environment is calm, consistent and appropriate, there are multiple research studies showing that there may be less need for medications. First line medication choice should never be neuroleptics or benzodiazepines unless the patient is in imminent danger of harming themselves or others because of the risk of delaying their cognitive recovery. Getting ahead of a crisis situation is critical and could mean using antidepressants, beta blockers and mood stabilizers early in the patient’s treatment in an attempt to avoid need for neuroleptic use. If neuroleptics are used, SGA are to be used first as there are less reported side effects that can be significantly detrimental to the recovery of the patient. There are conflicting reports of what specific medications are effective, but there are
limited large scale, quality human trials done that would demonstrate consistent patterns of effectiveness with any pharmacological treatment. The FDA has not approved any medications for behavioral disturbances in this population and most of what providers and researchers recommend for off-label use is based on animal studies or case reports done without much scientific backing or standardization. Guidelines for treating this population are still being developed and changed as more research is being done; this complicated illness can be tough on providers, patients and their families but more research needs to be done to expedite recovery and better preserve patient and caregiver safety.
References


