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Review

Psychotropics and Neuroprotection: Literature Review and Case Series Report

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Abstract

Agitation is a common manifestation of acute brain injury. When not addressed, agitation can lead to slower recovery rates, including delayed admission to acute rehabilitation programs. Antipsychotics are commonly used to control agitation in acute brain injury in the ICU. However, there is no current consensus on the most "efficacious and safest strategy" for use of antipsychotics in acute TBI. Haloperidol is arguably the commonly used antipsychotic for agitation in ICU setting at present. Interestingly, there are no studies to our knowledge that assess for haloperidol use in TBI patient's specifically. Further, there are some concerns with the use of Haloperidol given that it does not offer a neuroprotective effect and may have some adverse effects that are particularly harmful for this population. In this paper, we offer a review of alternate medications that may be more appropriate for the treatment of

agitation in acute brain injury, with less aversive effects. One stand out alternative is Valproic Acid. Aside from its anti-epileptic benefit, which is important in this population, valproic acid outshines other agents in that it has been shown to also be neuroprotective and offer anti-oxidant benefits. Aripiprazole may also be considered given that it has been found to be neuroprotective and reduce oxidative stress. Other medications such as olanzapine, risperidone, paliperidone, lithium, pramiprexole, and ziprasidone have shown to be either neuroprotective or have antioxidant properties. Quetiapine also shows promise. Case studies are also provided.

Keywords
Traumatic brain injury; neurotoxicity; neuroprotection; anti-psychotics; anti-epileptics

1. Background

Agitation is a common manifestation of acute brain injury, particularly in the early stages of injury. However, studies on the use of pharmacological agents for the control of agitation in this population remain extremely limited. Most studies available are animal studies or based on subjective observation. There is no current consensus on the most "efficacious and safest strategy" for use of antipsychotics in acute TBI [1]. Williamson et al. note in their 2016 study that a 'safe and effective treatment for agitation, which does not interfere with neurological recovery, remains to be identified". As such, this study aims to provide information that leads to a greater understanding of what pharmacological agents are most advantageous for this population.

Consequences of agitation include harm to self or others, use of chemical and physical restraints, increased length of stay in acute care, and decreased functional independence [2]. Agitation has also been associated with delays in recovery, including delayed admission to acute rehabilitation programs. Antipsychotics are commonly used to control agitation in acute brain injury in the ICU. Interestingly, there are no studies to our knowledge that assess for haloperidol use in TBI patient's specifically [2]. Haloperidal, arguably the commonly used antipsychotic for agitation in ICU setting, does not offer a neuroprotective effect and may have some adverse effects that are particularly harmful. Specifically, the use of haloperidol in acute TBI has been associated with: neuroleptic malignant syndrome (NMS), reduced seizure threshold, impaired long-term cognitive recovery [2], and neuronal loss [3]. Studies have also shown: a longer length of posttraumatic amnesia, delayed cognitive recovery, and increased incidences of behavioral and cognitive deficits [4].

2. Methods

PubMed database and reference lists from relevant articles were reviewed. We reviewed articles obtained through the PubMed to identify additional articles pertinent to neuroprotection.

3. Results

3.1 Neuroprotection versus Neurotoxicity

Severe hypoglycemia causes hippocampal damage [5, 6] activation of the N-methyl-d-aspartate, glutamate neurotoxicity, anoxic neuronal death and Amyloid-β neurotoxicity are implicated [7, 8]. Animal model shows, Memantine, offering neuroprotective effects in hypoglycemic rats [9]. TBI leads neurochemical alterations [10] Similar to hypoglycemic injury, glutamatergic system is implicated [11, 12] oxidative stress is also implicated [13] antioxidants has proved to be beneficial [14, 15].

3.2 Sedative Agents and Neuroprotection

When these patients are in acute status, it is important to know about medication with neurotoxic effect and neuroprotective effect. Available information are mostly from animal studies.

Propofol is reported to be neurotoxic [16, 17]. During acute brain injury and related complications, patients could get intubated and propofol's neuropsychiatric effect should be taken into consideration. Dexmedetomidine, another medication commonly used for sedation during intubation is considered to have neuroprotective effect [18-20].

3.3 Anti-Psychotics and Neuroprotection

During intubation and after extubation, antipsychotics are commonly given for agitation. In neuropsychiatric patients and traumatic brain injury, it is important to be knowledgeable about agents reported to carry neuroprotective effect. Haloperidal, the commonly used antipsychotic for agitation in ICU setting reportedly does not offer neuroprotective effect. In an animal study comparing neuroprotective effect of haloperidol and aripiprazole, haloperidol caused neuronal loss while aripiprazole offered neuroprotection [3].

Among the mechanism of neuroprotection is the 5-HT1A agonism [21-23]. 5-HT1A agonists might be beneficial in brain trauma [21, 22]. Atypical antipsychotics agents with 5-HT1A agonist properties may protect against excitotoxic injury and be safely used against TBI-induced agitation. Research suggests that atypical antipsychotics, agents with 5-HT1A agonist properties, may protect against excitotoxic injury and be used safely to reduce TBI-induced agitation [21, 23, 24]. It has been shown, in mice, that aripiprazole, ziprasidone but not haloperidol can protect against exicitotoxicity in vivo and their neuroprotective activity is antagonized by the selective 5-TH1A antagonist Way 100635 [23, 25, 26].

Olanzapine, aripiprazole, and ziprasidone have protective properties against oxidative stress, but not haloperidol [27]. This study measured effects of N-methyl-4-phenylpyridinium MPP(+) on cell viability, reactive oxygen species (ROS), superoxide dismutase (SOD). Olanzapine and aripiprazole reversed all the effects of MPP(+) treatment; Ziprasidone changed ROS and SOD but did not influence cell viability while haloperidol did not affect any of these effects [27]. Another study compared the neuroprotective effects of haloperidol, risperidone and paliperidone. In this study, haloperidol decreased cell viability and induced cell death while risperidone and paliperidone offered protection against it. However, strongest neuroprotective effect was seen in paliperidone [28].

Olanzapine and quetiapine protects cells from oxidative stress [29] Aripiprazole recovered decreased cell viability [30]. Aripiprazole offers neuroprotection [31, 32]. Quetiapine reversed the stress-induced suppression of hippocampal neurogenesis [33]. In a comparative study of anti-oxidant properties, OLA showed the highest antioxidant activity, followed by clozapine and Aripiprazole. In this study, quetiapine, risperidone, ziprasidone, and haloperidol showed minimal or no antioxidant activity [34].

In a study that evaluated oxidative damage in rat brain, olanzapine and aripiprazole did not induce oxidative damage as observed after haloperidol and clozapine [35]. More studies are needed to see if Olanzapine and aripiprazole offers the best neuroprotection followed by quetiapine, paliperidone, Risperidone and Ziprasidone. Newer agents Asenapine, lurasidone, Brexpiprazole, and cariprazine are also reported to offer neuroprotection [36-38]. Lurasidone, Brexpiprazole, and cariprazine are newer agents and their efficacy in agitation management needs more evidence. We identified two studies comparing neuroprotective effect of cariprazine and aripiprazole. In one study, cariprazine and aripiprazole blocked increase in glutamate, but cariprazine was more potent than aripiprazole (5-fold) [39]. In another study, both Cariprazine and aripiprazole decreased PCP-induced attention deficits [40].

3.4 Cognitive Enhancers and Neuroprotection

Memantine is approved by FDA for treating Alzheimer's dementia. To assess the neuroprotective effect of memantine in TBI, memantine was administered to rats after induced TBI and it prevented the neuronal loss [41]. Memantine offered neuroprotective activity against oxidative stress [42].

There are reports on the anxiogenic effect of Memantine and this could be a challenge during agitation management [43]. In a study of Memantine for depression, memantine produced an early anxiogenic response, but the effect is limited [44]. Memantine is effective in patients with agitation related to Alzheimer's disease [45].

Donepezil, another cognitive enhancer, approved by FDA for treating alzheimer’s dementia offers Neuroprotection against glutamate excitotoxicity [46].

3.5 Anti-Epileptics and Neuroprotection

Valproic acid could be a very good option in agitation management in delirium related to TBI [47, 48]. Apart from its anti-epileptic effect in TBI patients, it offers neuroprotection [49, 50]. It has anti-oxidant effect. Valproic acid’s antioxidant effect is better when compared to carbamazepine and phenobarbital [51]. In addition to lithium, it offers anti-oxidant and neuroprotective effects [52, 53]. Exposure to valproic acid in utero increases the risk of major congenital malformations including neural tube defects, spina bifida, developmental delay, cognitive impairment [54] and autism [55]. For agitation management in delirium related to TBI in women of child bearing age, atypical antipsychotics should be considered first. Pregnancy test is required.

Similarly, Levetiracetam, lacosamide and zonisamide offers neuroprotection and needs to be considered when seizures are co-morbid or for seizure prevention [56-59]. Lamotrigine has neuroprotective and anti-oxidant effect [60-62]. Levetiracetam, lacosamide and lamotrigine are not good options in acute management. In an animal study on neuroprotective and neurotoxic effects of carbamazepine and oxcarbazepine, toxic effect like apoptosis was identified. In this study,

these drugs also did not protect hippocampal neurons from toxicity related to ischaemia. However, it is important to note that this toxic effect was not mediated by N-methyl-D-aspartate (NMDA) [63]. In a study measuring Oxidative Status, Carbamazepine caused oxidation [64].

3.6 Carbamazepine, Oxcarbazepine, Gabapentin, Pregabalin, Phenobarbital, Phenytoin

Li et al reported that the oxidative stress and impairment of the antioxidant was evident after 2 hours exposure to Carbamazepine [65, 66]. In a study comparing the oxidative status of Valproic Acid Carbamazepine, and Phenobarbital, there was better regulation of oxidant and antioxidant status in valproic acid group compared to phenobarbital and carbamazepine [51]. Oxcarbazepine which is related to Carbamazepine also is reported to affect antioxidant systems [67].

3.6.1 Gabapentin

There are varying reports on gabapentin and neuroprotective effect.

Anti-NMDAR encephalitis presents with psychiatric disturbances and cognitive deficits and could lead to rapid progression to catatonia and autonomic instability. Lithium, Gabapentin and Valproic acid could help in mood symptoms [68, 69]. In Anti-NMDAR encephalitis, glutamate activation of GABAergic neurons is decreased leading to reduced GABA activity causing significant glutamatergic hyperactivity and neuropsychiatric symptoms of anti-NMDA receptor encephalitis [70]. Gabapentin enhances the release of GABA [71]. Gabapentin offers protection against glutamate-induced neuronal injury [72]. However, a study reports that gabapentin decreases brain antioxidant enzymes [73]. There is one study reporting that gabapentin may be blocking new synapse formation [74].

Antioxidant effect was not observed in Pregabalin [75]. Phenobarbitol has antioxidant and neuroprotective effects [76]. Phenytoin is reported to induce oxidative stress [77, 78].

3.6.2 Ketamine

Ketamine and neuroprotection: Intra nasal Ketamine FDA approved for depression. It is used in anesthesia and pain management. Ketamine exerts neuroprotection via attenuating inflammation [79, 80].

3.7 Lithium and Neuroprotection

Lithium has great neuroprotective effect [81]. Lithium's neuroprotective effects on TBI are by stimulating neurogenesis, modulating inflammatory cytokines, inhibiting glycogen synthase kinase and reducing neuronal death [81]. Lithium is neuroprotective and prevent neuronal apoptosis [82, 83].

3.7.1 Pramipexole, Amantadine, Benzodiazepines, Trazodone

Pramipexole has neuroprotective effect against glutamate-induced neurotoxicity [84]. Amantadine leads to recovery and decreases dopamine-release deficits in TBI patients [85, 86]. Chronic use of benzodiazepines offers no neuroprotection while immediate administration after ischemia is neuroprotective [87]. An animal study identified oxidative damage caused by

methylphenidate [88]. Trazodone, commonly used for insomnia has neuroprotective effects on the frontal cortex, hippocampus and dentate gyrus [89].

3.7.2 Buspirone and Neuroprotection

Buspirone is a5-HT1A partial agonist and provide benefit in TBI. In a study combining environmental enrichment and Buspirone, memory retention and spatial learning were enhanced [90].

4. Alternatives to Haloperidal in Practice: Case Studies

Patient 1: 49 year-old male, found seizing at home, hypoglycemic to 28, somnolent with Glasgow Coma Scale of 5. MRI: no evidence of acute process. He exhibited waxing and waning mental status with periods of agitation, saying incomprehensible words. On examination, gaze darting around room and he exhibited nonsensical garbled speech. Aripiprazole and Valproic acid were started. Agitation decreased and patient was transferred to neurocognitive rehabilitation.

Patient 2: 55 year-old female with anoxic brain injury after a hypoglycemic episode four weeks prior to admission. The patient was not oriented to person, place, or time, and exhibited unpredictable and violent behavior. She responded to most questions inappropriately, with illogical phrases many neologisms. Aripiprazole and Donepezil were started, agitation and violent behavior decreased and she was discharged to rehabilitation.

Patient 3: 42-year-old male with a past medical history of hypertension was involved in a motor vehicle crash. He was in hospital for 48 day mostly for agitation. After motor vehicle crash, patient had a Glascow Coma Scale of 7T and he was intubated. MRI Brain revealed bilateral occipital subdural hematoma, small right occipital contusion and Left frontal subdural hygroma. Neurosurgery was consulted for ICH coup contra coup type brain injury with left frontal subdural hygroma, bilateral occipital subdural hematoma and a small right occipital intra-parenchymal hemorrhage with suspected diffuse axonal injury. He was transferred back and forth to the ICU for safety and medication management for agitation. For several days, he was continually agitated, hitting head on side rails/light fixtures requiring haloperidol injection every four hours and quetiapine 4 times daily. He was on restraints. Psychiatry was consulted, Haloperidol and quetiapine were discontinued. Aripiprazole 5mg Qam and 7.5mg Qpm was started and Haloperidol prn was replaced by Ziprasidone 5mg Q6hrs PRN. Valproic Acid started and increased to 750mg po or IV bid. Memantine was added Day 43. He was much more calm and rational (able to carry on a conversation). He still exhibited episodic agitation. Aripiprazole changed to Asenapine. Ziprasidone 5mg Q6hrs PRN was changed to Olanzapine5mg IM q4h PRN. Memantine stopped to avoid polypharmacy. Significant progress was made, and patient was off restraints. CT head and EEG were without complication. He slept mostly through the night. He was ambulating with staff, and was using the bathroom on his own. He worked well with therapy and he ate all of his meals. Patient was cooperative and willing to participate throughout session. Patient was able to complete functional mobility to and from his room to the therapy gym with minimal verbal cuing to complete the task suggesting improvements with safety awareness and balance. As his agitation decreased, he was transferred to an outside neuro cognitive rehabilitation center.

5. Conclusion

Acute agitation in traumatic brain injury is a common occurrence in the ICU. However, there is no consensus regarding the best pharmacological agents for this population. At present, Haloperidol is commonly used to control agitation in this population. However, research shows that the adverse effects of haloperidol may outweigh the benefits. This review provided a number of alternate medications that have not only been shown to reduce agitation, but also offer neuroprotective effects, antioxidant effects, or both. Given that acute agitation in traumatic brain injury has been associated with a longer course of recovery, particularly when Haloperidol is used for an extended period, the hope is to provide alterative agents that will not only improve agitation, but also lead to improved overall outcomes in traumatic brain injury. Studies are needed in this area.

Author Contributions

All authors did the literature review, preparation of manuscript, edition.

Competing Interests

The authors have declared that no competing interests exist

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