ABSTRACT

Pharmacological Interventions for Treating Cognitive and Behavioral Impairments Following Traumatic Brain Injury

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Traumatic Brain Injuries (TBI) occur when a blow to the head results in the alteration of brain functioning. While many people with mild TBI are able to recover within a few weeks, symptoms and impairments can be long-term, lasting months to years, or be lifelong, and millions of individuals around the world live with a permanent TBI-related disability. Some of the more common persistent post concussive symptoms include headaches, depression, fatigue, impaired cognitive functioning, poor memory, attention/concentration difficulties, anxiety, aggression/irritability, difficulty regulating emotions, and sleep disturbances. This literature review examines recent research on various pharmacological treatment options that address the manifestation of TBI symptoms, with emphasis on addressing cognitive and behavioral deficits. Literature suggests that pharmaceutical options are the most widely available treatment for many TBI symptoms, but are often limited in their flexibility, indicating further investigation into a comprehensive treatment is necessary.

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PHARMACOLOGICAL INTERVENTIONS FOR TREATING COGNITIVE AND BEHAVIORAL IMPAIRMENTS FOLLOWING TRAUMATIC BRAIN INJURY

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CHAPTER ONE

Introduction

Traumatic Brain Injuries (TBI) occur when a blow to the head results in the alteration of brain functioning. Although the majority of people with mild TBI recover within a few weeks, symptoms and impairments can be long-term, lasting months to years, or be lifelong. TBI severity can be classified by the amount of time loss of consciousness (LOC) is experienced. A mild TBI is defined by an LOC of 30 minutes or less, an LOC of 30 minutes to 24 hours corresponds to a moderate TBI, and an LOC of over 24 hours is considered a severe TBI (Brasure et al., 2012). An estimated 19 million individuals in Europe and North America live with a permanent TBI-related disability (Tenovuo, 2005). Some of the more common persistent post concussive symptoms include headaches, depression, fatigue, impaired cognitive functioning, poor memory, attention/concentration difficulties, anxiety, aggression/irritability, difficulty regulating emotions, and sleep disturbances (Bryan, 2013; Chin & Zeber, 2020; Dean & Sterr, 2013; Ellis et al., 2015; Kalmbach et al., 2018; Patil et al., 2011; Zuckerman et al., 2016). These symptoms can be detrimental to both daily functioning and long-term health (Bryan & Clemans, 2013; Ellis et al., 2015; Lange et al., 2014). Although research has identified strategies to help manage some of these symptoms individually, no solutions can simultaneously address all dimensions of TBI symptomatology. Many of the TBI treatments currently used target a specific symptom or subset of symptoms, typically the most prevalent or disabling, and are based on treatments for other conditions with a

similar major symptom. For example, one option that is being investigated for the treatment of attention deficits in TBI patients is the use of stimulants, which are used to treat the symptoms of attention deficit hyperactivity disorder (ADHD).

Recovering from a TBI is crucial for both the return to daily life, and the integrity of long-term health. One symptom of TBIs that may persist is sleep disturbances. Sleep has been shown to play a crucial role in both the healing process and overall health following TBI (Kalmbach et al., 2018). Persistent sleep disturbances following TBI may have significant effects on daily functioning and overall long term health, and must therefore be addressed in order to give the patient the best chance at recovery. TBI can have many other long term effects on one's health and well being. TBI patients are at higher risk for developing dementia, have higher rates of depression, and are more likely to attempt suicide (Barnes et al., 2018; Bryan & Clemans, 2013; Chin & Zeber, 2018). These are all major issues that need to be addressed in treating TBI patients.

An area of focus in the literature for traumatic brain injury treatment is the use of pharmaceuticals. Many of the identified medications are adapted from use in other conditions with a similar symptom profile. Due to this, many of the pharmaceuticals address an individually targeted symptom or set of symptoms. This review will look at five main categories of pharmaceutical treatments used, including psychostimulants, antidepressants, Alzheimer's / Dementia medications, Anti-Parkinson's medication, and atypical antipsychotics.

CHAPTER TWO

Methods

For this literature review, both systematic and unsystematic search methods were utilized. For the systematic searching, a Boolean search was completed in PubMed using the search terms ((TBI) OR (traumatic brain injury) OR (concussion) OR (brain injury)) AND ((pharmacological) OR (drug) OR (medication)), resulting in 8,919 results. The species specific filter of "Humans" was added to eliminate animal studies, bringing the results down to 4,702. Since TBI research has improved exponentially in the last two decades, the next filter applied was restricting articles based on publication year, only including those that have been published in 2000 or later, to ensure data was up to date and still relevant. This narrowed the number of articles down to 3,993. These articles were then examined based on title, and articles of interest moved on to have their abstract investigated. From here, articles were either included or discarded based on meeting three criteria: 1) the article must be published in a peer-reviewed journal; 2) the study must involve a pharmacological treatment for traumatic brain injury; 3) the study must include quantitative data.

Additional articles were identified through unsystematic methods. Targeted search terms were run through Google Scholar to find more specific articles as needed. For example, the search terms "traumatic brain injury" and "methylphenidate" and "cognition" were used to find articles involving the use of methylphenidate for improving cognition following traumatic brain injury. Articles were also identified through related

sources, either from the references page of an article being used, or through the “cited by” feature on Google Scholar, which identifies other papers that have cited the article in question. Similar unsystematic methods were used to identify supplemental articles used in sections such as background information, alternative treatments, and long term outcomes of traumatic brain injuries.

CHAPTER THREE

Results

Many of the studies that involve using pharmaceuticals to treat traumatic brain injury are completed through either clinical trials or as routine clinical practice. Included in these are randomized, double-blind, placebo-controlled trials; comparative drug trials; preliminary, flexible-dose, open-label trials; and findings from routine clinical use in treating patients. This section will review five main categories of pharmaceutical treatments used: psychostimulants, antidepressants, Alzheimer's / Dementia medications, Anti-Parkinson's medication, and atypical antipsychotics.

Psychostimulants

Psychostimulants are typically used to improve cognitive and behavioral functioning in patients with Attention Deficit Hyperactivity Disorder (ADHD). They have been proposed as a possible treatment option for targeting TBI-induced cognitive deficits, including memory loss, forgetfulness, trouble concentrating, and difficulty with problem solving or decision making. Two of these psychostimulants that have been used to treat TBIs are methylphenidate and dextroamphetamine. Methylphenidate has been the subject of numerous studies to evaluate its effectiveness in the treatment of TBI, and has had mixed results (Talsky et al., 2011). Research has found that at one month post injury, methylphenidate improves concentration and memory task performance. However, these effects dissipate by the three month mark, suggesting only acute benefits. In a

review of the chronic use of methylphenidate after TBI, Talsky and colleagues (2011) found that the literature was contradictory with some demonstrating a notable improvement in attention, and others stating no neurobehavioral benefit. Lee and colleagues (2005) compared methylphenidate against a placebo for treating neuropsychiatric sequelae in TBI patients. This double-blind, placebo-controlled, comparative drug trial compared methylphenidate against both placebo and the Selective-serotonin reuptake inhibitor sertraline, in a group of 30 mild to moderate TBI patients, who were between 2 weeks and one year post-injury. Methylphenidate was found to be significantly more effective than placebo in treating depressive symptoms, but methylphenidate and placebo had comparable improvement in cognitive functioning (Lee et al., 2005). Johansson et al. (2017) investigated the effects of methylphenidate on the long-term post-concussive symptoms of mental fatigue and poor cognitive functioning following a TBI. This study included 30 patients who suffered from long-term post-concussive symptoms following mild to moderate TBI, who had previously reported positive effects with methylphenidate treatment during the initial 3-month intervention (phase A). This follow-up study (phase B) followed these patients for an additional 6 months of methylphenidate treatment. When compared to baseline, treatment with methylphenidate improved ratings of mental fatigue, depression, and anxiety, as well as improving participant's processing speed, attention, and working memory. This was a continuation of a previous study, and therefore only used participants who had positive results in the first portion of the study (Johansson et al., 2017). For this reason, caution should be used when evaluating these results, and conclusions on the effect of methylphenidate in TBI patients cannot be unequivocally drawn from this study.

Another psychostimulant that has been investigated is dextroamphetamine. Hart et al. (2018) completed a preliminary study comparing the effects of dextroamphetamine to placebo on a wide range of cognitive and behavioral functions in patients with moderate to severe TBI. This study was a double-blind, randomized controlled trial, and participants were 32 patients of a specialized inpatient TBI rehabilitation unit who were less than 6 months post-injury. No statistically significant differences were identified between the dextroamphetamine group and placebo group (Hart et al., 2018).

Antidepressants

TBI patients have been found to have decreased cerebral levels of dopamine and serotonin, which suggests the use of antidepressants for treating TBI could be effective (Vecht et al., 1975). Sertraline, which belongs to the class of antidepressant medications known as selective serotonin reuptake inhibitors (SSRIs), has been suggested as a successful treatment for depressive symptoms following TBI (Fann et al., 2000). Lee and colleagues (2005) examined the effects of sertraline compared to placebo in treating TBI. This double-blind, placebo-controlled, comparative drug trial compared methylphenidate, sertraline, and placebo in a group of 30 mild to moderate TBI patients, who were between 2 weeks and one year post-injury. While sertraline was found to significantly improve depressive symptoms, it failed to show improvements in cognitive functioning. Additionally, sertraline decreased cognitive function versus placebo, which led the authors to suggest that it may be worth exploring if sertraline has a potential hindering effect on healing in TBI patients (Lee et al., 2005).

Alzheimer's / Dementia Medications

Dementia is the broad clinical syndrome characterized by the loss of cognitive functioning that disrupts daily functioning and quality of life (Geldmacher & Whitehouse, 1996). Alzheimer's disease is a type of dementia, diagnosed by memory impairment and loss of at least one other cognitive function (Castellani et al., 2010). One common chronic symptom of TBI is cognitive deficits, including memory impairment and disrupted daily functioning. Medications that treat Alzheimer's and dementia may therefore alleviate TBI-induced cognitive impairments.

Kim et al. (2010) investigated the effects that the Alzheimer's medication memantine had on cerebral glucose metabolism and cognitive functioning in patients with TBI-induced cognitive impairments. The authors compared F-18 fluorodeoxyglucose positron emission tomography (F-18 FDG-PET) study analyses done before and after memantine therapy in 17 patients with posttraumatic cognitive impairment. Following eight weeks of treatment, overall cognitive functioning was found to significantly improve with memantine treatment. Specifically, the authors evaluated individual subitems of cognition, and observed significant improvement in attention and calculation, as well as language. However, no significant improvement was seen in the subitems of orientation, registration, or recall. Significant changes were also identified in cerebral glucose metabolism, which reflects changes in neuronal activation.

Since many brain functions affected by TBI are at least partly cholinergically mediated, it has been proposed that another class of Alzheimer's medication, central acetylcholinesterase inhibitors (CAIs), may be able to alleviate some of these cognitive deficits (Tenovuo, 2005). As part of routine clinical practice, Tenovuo (2005)

investigated the use of three CAIs to improve daily functioning in the treatment of mild to severe chronic TBI: donepezil, galantamine, and rivastigmine. Patients included in this study had chronic sequalae of a TBI, were approximately one year or longer post-injury, and had at least one of the four target symptoms (fatigue, poor memory, diminished attention, or problems with initiation) clinically attributed to their TBI. CAIs were prescribed to 111 patients, and overall, 61% of patients had a positive response to at least one of the CAIs, and therapeutic responses were observed quickly and at low doses. Measures were based on subjective descriptions of symptoms and side effects during a thorough clinical interview.

Anti-Parkinson's Medications

The antiparkinson drug amantadine increases the level of dopamine in the brain, and therefore may be useful in the treatment of TBI (Talsky et al., 2011). Amantadine has been shown to be successful in both acute and chronic phases of TBI treatment, especially in addressing cognition difficulties and agitation (Talsky et al., 2011). Approximately 29-69% of TBI patients experience lasting irritability, which can be a significant detriment to interpersonal relationships (Hammond et al., 2015). Hammond et al. (2015) investigated the effects of amantadine compared to placebo on post-acute TBI-induced irritability. Participants were 168 post-TBI patients with irritability who were at least 6 months post-injury. This study was a 60 day parallel-group, randomized, double-blind, placebo-controlled trial. In this study, substantial improvement in irritability was observed in both the amantadine and placebo groups, but the difference between the amantadine and placebo groups was not significant (Hammond et al., 2015). While no significant benefit was identified in treating irritability, there were significant

improvements in cognitive and behavioral impairments (Hammond et al., 2015). Additional studies have observed improvements in motivation, attention, concentration, alertness, and executive functioning, and reduction in processing time, agitation, distractibility, fatigue, aggression, and anxiety (Talsky et al., 2011).

Atypical Antipsychotics

Up to 71% of TBI patients experience TBI-induced aggression; the atypical antipsychotic quetiapine has been effective in reducing aggression in conditions such as schizophrenia, and has therefore been proposed in the treatment of TBI-induced aggression (Kim & Bijlani, 2006). A preliminary, flexible-dose, open-label study conducted by Kim & Bijlani (2006) investigated the efficacy and tolerability of quetiapine to treat TBI-induced aggression in seven patients. The results found that quetiapine was both well-tolerated and led to significant reductions in aggression (Kim & Bijlani, 2006).

CHAPTER FOUR

Discussion and Conclusions

A benefit of using pharmaceuticals in the treatment of traumatic brain injuries is the ability to target the specific symptom being addressed. These medications are promising, because they have already been shown to be effective in treating this symptom in another condition. This can also be a disadvantage, however, as pharmaceuticals are typically only successful in addressing one symptom or subset of symptoms (typically the patients most concerning/debilitating), and are not able to address the large range of symptoms TBI patients face.

Psychostimulants

Methylphenidate has had very mixed results. Talsky et al. (2011) found that methylphenidate improved concentration and memory task performance one month post-injury, but no longer at three months post injury. This suggests that methylphenidate only has acute benefits post-traumatic brain injury. Talksy and colleagues (2011) reviewed the literature on chronic use of methylphenidate after TBI, and found it to be contradictory, as some studies demonstrated a notable improvement in attention, and others stating no neurobehavioral benefit. These conflicting results of chronic use indicate that more research should be done to verify the timeline in which the acute benefits begin to dissipate. Lee and colleagues (2005) found that methylphenidate was significantly more effective than placebo in treating depressive symptoms, but did not improve cognitive

functioning in TBI patients. This study brings the complexity of TBI symptoms into the discussion on methylphenidate, and warrants further investigation. Johansson et al. (2017) found that in TBI patients with long-term post-concussive symptom, treatment with methylphenidate improved ratings of mental fatigue, depression, and anxiety, as well as improved participant's processing speed, attention, and working memory. While this sounds like promising results, this was a continuation of a previous study and only included the participants who had positive results in the first portion. For this reason, caution should be used when evaluating these results, and conclusions on the effect of methylphenidate in TBI patients cannot be unequivocally drawn from this study.

Hart et al. (2018) compared the effects of dextroamphetamine to placebo in TBI patients during a preliminary study. No statistically significant differences were identified between the dextroamphetamine group and placebo group. This study does not offer much promise for the use of dextroamphetamine in TBI patients.

Antidepressants

Lee and colleagues (2005) investigated the effects of the selective serotonin reuptake inhibitor (SSRI) sertraline compared to placebo in TBI patients, and sertraline was found to significantly improve depressive symptoms. While this appears to be promising evidence for the use of sertraline in TBI patients, the study also found results that suggest it may do more harm than good. Sertraline not only failed to improve cognitive functioning, but actually decreased cognitive function compared to placebo. For this reason, the authors suggest it may be worth exploring whether sertraline has a potential hindering effect on healing (Lee et al., 2005). Due to sertraline's possible

detriment to the natural recovery process, any further research should proceed cautiously.

Alzheimer's / Dementia Medications

Kim et al. (2010) investigated the effects of the Alzheimer's medication memantine on cerebral glucose metabolism and cognitive functioning in patients with TBI-induced cognitive impairments. Following eight weeks of treatment, overall cognitive functioning was found to significantly improve with memantine treatment, and significant changes were identified in cerebral glucose metabolism, which reflects positive changes in neuronal activation. This shows promising evidence for the continued investigation into the use of memantine in treating TBI patients.

Tenovuo (2005) used three central acetylcholinesterase inhibitors (CAIs) to treat TBI patients as part of routine clinical practice. Donepezil, galantamine, and rivastigmine were used to improve daily functioning of 111 patients being treated for chronic TBI, and 61% of patients had a positive response to at least one of the CAIs based on subjective interview responses. This provides evidence that this class of medications may be worth investigating for the treatment of chronic TBI. Additionally, therapeutic responses were observed quickly and at low doses. This could be a promising option for patients to see benefits quickly, and central acetylcholinesterase inhibitors (CAIs) should be further investigated as a possible treatment option for daily functioning deficits following TBI.

Anti-Parkinson's Medications

The anti-Parkinson drug amantadine has been shown to be successful in both acute and chronic phases of TBI treatment, especially in addressing cognition difficulties

and agitation (Talsky et al., 2011). This supports its further investigation for the use of treating traumatic brain injury, especially in patients experiencing both cognitive difficulties and agitation. Hammond et al. (2015) investigated the effects of amantadine compared to placebo on post-acute TBI-induced irritability. In this study, both the amantadine and placebo groups demonstrated substantial improvement in irritability, but the difference between these two groups groups was not significant (Hammond et al., 2015). While no significant benefit was identified in treating irritability, there were significant improvements in cognitive and behavioral impairments (Hammond et al., 2015). Additional studies have observed improvements in motivation, attention, concentration, alertness, and executive functioning, and reduction in processing time, agitation, distractibility, fatigue, aggression, and anxiety (Talsky et al., 2011). These medications should be further investigated for their ability to treat cognitive and behavioral impairments following traumatic brain injuries.

Conclusions

While there have been many investigations into the use of pharmacological interventions for treating cognitive and behavioral impairments following traumatic brain injury, many questions remain in the field. Some of the stronger research designs have included being double blind, placebo controlled, randomized, or control trials. Weaker research designs included aspects such as flexible dose, open label, or reflections of routine clinical practice. Difficulties in conducting research in this area include the hardships of recruiting patients, contraindications due to current treatments, and the uniqueness of each individual brain injury. Many of these medications have shown promising results in achieving at least partial symptom relief, but there is still no great

option for treating the broad range of TBI symptoms. Methylphenidate has had very mixed results, but may be beneficial in improving depressive symptoms and cognitive functioning. Sertraline has been shown to improve depressive symptoms in TBI patients, but may impair cognitive functioning and possibly hinder the recovery process. Memantine has shown very promising results in improving cognitive functioning in TBI patients, and is worthy of attention for future research studies. Subjective patient reports of central acetylcholinesterase inhibitors use suggest possible improvement in fatigue, memory deficits, attention deficits, and/or initiation problems. Amantadine may not aid in improving irritability, but may be beneficial in improving cognitive and behavioral deficits. Preliminary studies of quetiapine have shown improvement in TBI-induced aggression. Additionally, many of these medications are quite intense, and typically come with heavy side effects. There are still millions of individuals living with unresolved symptoms from TBI, therefore further investigations into safe and effective treatment options for TBI are necessary.

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