Are Stimulants Beneficial In Individuals with Traumatic Brain Injury?

Rajesh R Tampi* and Michael B Maksimowski

Department of Psychiatry, MetroHealth, Cleveland, Ohio, USA

*Corresponding author: Rajesh R Tampi, Professor of Psychiatry, Case Western Reserve University School of Medicine, Vice Chairman for Education Program Director, Psychiatry Residency, Department of Psychiatry, MetroHealth, 2500 Metrohealth Drive, Cleveland, Ohio, 44109, USA, Tel: (203) 809 5223; E-mail: rajesh.tampi@gmail.com

Rec date: Dec 15, 2015; Acc date: Dec 18, 2015; Pub date: Dec 25, 2015

Copyright: © 2015 Tampi RR, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

Traumatic Brain Injury (TBI) can be defined as an insult to the brain from an external mechanical force that can result in temporary or permanent impairments in cognitive, functions and behaviour [1]. It is estimated that an average of 1-2 million individuals each year sustain a TBI in the United States [2,3]. The physical, cognitive and behavioral limitations experienced from TBI often become chronic, impacting an individual’s daily functioning, relationships and employment [4].

Despite our knowledge of the epidemiology, pathophysiology, and multifaceted consequences of TBI, there is no standardized protocol or FDA-approved medication to pharmacologically treat cognitive and behavioral symptoms associated with TBI [5]. Warden et al. completed a comprehensive literature search and did not find sufficient evidence to support any treatment standards [6]. Multiple studies have shown effectiveness of SSRIs and stimulants for treatment of depressive and cognitive symptoms associated with TBI, respectively [7]. The theoretical basis for studying stimulants in individuals with TBI has always been the large body of research supporting efficacy of stimulants in individuals with Attention Deficit Hyperactivity Disorder (ADHD) [8].

Dopamine is considered an essential neurotransmitter in attention processing [9]. Stimulants are known to enhance dopaminergic activity within many brain areas but especially within the striatum and frontal cortex, regions theorized to be essential for attention [10]. TBI often results in damage to brain regions abundant with dopaminergic receptors as well as dopamine-producing areas [11]. This includes the frontal lobe, which is more susceptible to traumatic forces exerted by head injury than other lobes [12,13].

Evidence for Using Stimulants

A systematic review of PubMed, MEDLINE, EMBASE, PsycINFO and Cochrane collaboration from December 4, 2014, indicates that there are a total of sixteen RCTs on the use of stimulants in individuals with TBI. Of the sixteen studies, three studied pediatric populations [14-16]. The majority of studies assessed methylphenidate (MPH) [13,17-28] while one assessed dexamphetamine and MPH16, and one assessed modaflanil [29]. Over half of the studies utilized a cross-over design [14-16,24-29]. Patients ranged in severity of TBI from mild to severe, as well as in latency between TBI diagnosis and study treatment. Dosing of MPH ranged from one-time doses of 20 mg to twice-daily doses of 0.3 mg/kg. The one study that assessed dexamphetamine adhered to patients’ current dosing, which ranged from 5 to 10 mg twice daily. In the one study that assessed modaflanil, dosing began at 100 mg daily which was titrated to 400 mg daily over 14 days [29]. Quantitative measures included scales of arousal, depression, and behaviour, as well as attentional tasks to assess reaction time and accuracy. Fourteen of the 16 studies utilized placebo as the only comparator to stimulant. One study compared MPH to sertraline and placebo22 and another study compared MPH or dexamphetamine to placebo [16].

Seven studies showed significant improvements in reaction time [14,20,21,23-25] while four studies showed significant improvements in accuracy [20,21,24,27]. One study reported significant improvements in caregiver-reported attentional behavioral scales [24]. One study found significantly decreased length of hospital stay with treatment [19]. One study showed significant improvements in depressive symptoms [22]. One study found a significantly decreased duration of hospital stay for patients given MPH [19]. Only one of the three paediatric studies found a significant benefit (attention tasks) with stimulant use compared to placebo [15]. Two studies included follow-up; one found significant differences in disability ratings, attention-concentration, and motor memory at 30 days but not 90 days23, while the other found no significant differences between stimulant and placebo groups at 1 year.27 Of note, the majority of studies demonstrated significant treatment effects immediately (i.e., within minutes to hours) after first-time administration of the tested stimulant. Four of the sixteen studies (2 adult, 2 pediatric) did not find benefit for stimulants when compared to placebo [15,16,18,29]. Two studies found no significant differences in self-reported side effects [17,26] although one of the two studies showed a significant difference in mean arterial pressure [17].

Stimulants were well tolerated in thirteen of the sixteen studies with the side-effect profile of the drug being similar to that of placebo. Six studies did not comment on whether side effects were or were not observed.

Summary of Evidence

The available data from a systematic review of the literature indicates that stimulants can improve attention (speed of information processing, reaction time and task performance) in individuals with TBI, immediately and for a short term period. Stimulants were also noted to reduce length of hospital stay and improve depressive symptoms. These medications were fairly well-tolerated in the studies.

Based on our current review, it would be prudent to state that stimulants can be recommended for immediate and short term treatment of attentional deficits in individuals with TBI. However, it remains to be determined whether stimulants have any benefit on other cognitive domains, mood symptoms, anxiety symptoms or behavioral issues in individuals with TBI. Additionally, the long-term treatment efficacy of these drugs in individuals with TBI is not evident at the current time.
Conclusion

There is evidence to suggest immediate and short-term efficacy for psychostimulants in the treatment of attentional deficits in individuals with TBI. Stimulants appear to be well-tolerated in the majority of the studies included in this review. Data from well conducted larger and longer term RCTs will be helpful in determining whether stimulants have efficacy on different cognitive, behavioral and functional domains in individuals with TBI.

References

1. Capruso DX, Levin HS (2000) Neurobehavioral sequelae of head injury. Head injury. New York: McGraw-Hill: 525-553.
2. Thurman D, Guerrero J (1999) Trends in hospitalization associated with traumatic brain injury. JAMA 282: 954-957.
3. Thurman DJ, Alverson C, Dunn KA, Guerrero J, Sniezek JE (1999) Traumatic brain injury in the United States: A public health perspective. J Head Trauma Rehabil 14: 602-615.
4. Prigatano GP (1999) Principles of neuropsychological rehabilitation. Oxford University Press.
5. National GC. Traumatic brain injury medical treatment guidelines.
6. Neurobehavioral Guidelines Working Group, Warden DL, Gordon B, Brennan AR, Arnsten AF (2008) Neuronal mechanisms underlying cognitive, behavioral and functional domains in children with brain injury. Pediatr Neurosurg 29: 121-126.
7. Silver JM, McAllister TW, Arciniegas DB (2009) Depression and cognitive complaints following mild traumatic brain injury. Am J Psychiatry 166: 653-661.
8. National resource center on AD/HD. Managing Medication for Adults with ADHD Web site.
9. Brennan AR, Arnsten AF (2008) Neuronal mechanisms underlying attention deficit hyperactivity disorder: the influence of arousal on prefrontal cortical function. Ann N Y Acad Sci 1129: 236-245.
10. Schiffer WK, Volkow ND, Fowler JS, Alexoff DL, Logan J, et al. (2006) Therapeutic doses of amphetamine or methylphenidate differentially increase synaptic and extracellular dopamine. Synapse 59: 243-251.
11. Chudasama Y, Robbins TW (2006) Functions of frontalostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. Biol Psychol 73: 19-38.
12. Benson DE, Blumer D (1982) Psychiatric aspects of neurological disease. Greune & Stratton.
13. Clifton GL, Grossman RG, Makela ME, Miner ME, Handel S, et al. (1980) Neurological course and correlated computerized tomography findings after severe closed head injury. J Neurol Surg. 52: 611-624.
14. Mahalick DM, Carmel PW, Greenberg JP, Molosfky W, Brown JA, et al. (1998) Psychopharmacologic treatment of acquired attention disorders in children with brain injury. Pediatr Neurosurg 29: 121-126.
15. Williams SE, Ris MD, Ayyangar R, Scheff BK, Berch D (1998) Recovery in pediatric brain injury: is psychostimulant medication beneficial? J Head Trauma Rehabil 13: 73-81.
16. Nikles CJ, McKinlay L, Mitchell GK, Carmont SA, Senior HE, et al. (2014) Aggregated n-of-1 trials of central nervous system stimulants versus placebo for paediatric traumatic brain injury—a pilot study. Trials 15: 54.
17. Alban JP, Hopson MM, Ly V, Whyte J (2004) Effect of methylphenidate on vital signs and adverse effects in adults with traumatic brain injury. Am J Phys Med Rehabil 83: 131-137.
18. Hart T, Whyte J, Ellis C, Chervoneva I (2009) Construct validity of an attention rating scale for traumatic brain injury. Neuropsychology 23: 729-735.
19. Khalali HA, Keramatian K (2008) Effect of methylphenidate in patients with acute traumatic brain injury; a randomized clinical trial. Progress in Neurotherapeutics and Neuropsychopharmacology 3: 189-197.
20. Kim J, Whyte J, Patel S (2012) Methylphenidate modulates sustained attention and cortical activation in survivors of traumatic brain injury: A perfusion fMRI study. Psychopharmacology (Berl) 222: 47-57.
21. Kim YH, Ko MH, Na SY, Park SH, Kim KW (2006) Effects of single-dose methylphenidate on cognitive performance in patients with traumatic brain injury: a double-blind placebo-controlled study. Clin Rehabil 20: 24-30.
22. Lee H, Kim SW, Kim JM, Shin IS, Yang SJ, et al. (2005) Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. Hum Psychopharmacol 20: 97-104.
23. Plenger PM, Dixon CE, Castillo RM, Frankowski RF, Yablon SA, et al. (1996) Subacute methylphenidate treatment for moderate to moderately severe traumatic brain injury: A preliminary double-blind placebo-controlled study. Arch Phys Med Rehabil 77: 536-540.
24. Whyte J, Hart T, Schuster K, Fleming M, Polansky M, et al. (1997) Effects of methylphenidate on attentional function after traumatic brain injury. A randomized, placebo-controlled trial. Am J Phys Med Rehabil 76: 440-450.
25. Whyte J, Hart T, Vaccaro M, Grieb-Neff P, Risser A, et al. (2004) Effects of methylphenidate on attention deficits after traumatic brain injury: a multidimensional, randomized, controlled trial. Am J Phys Med Rehabil 83: 401-420.
26. Willnott C, Ponsford J, Olver J, Ponsford M (2009) Safety of methylphenidate following traumatic brain injury: Impact on vital signs and side-effects during inpatient rehabilitation. J Rehabil Med 41: 585-587.
27. Willnott C, Ponsford J (2009) Efficacy of methylphenidate in the rehabilitation of attention following traumatic brain injury: A randomised, crossover, double blind, placebo controlled inpatient trial. J Neurol Neurosurg Psychiatry 80: 552-557.
28. Gualtieri CT, Evans RW (1988) Stimulant treatment for the neurobehavioral sequelae of traumatic brain injury. Brain Inj 2: 273-290.
29. Jha A, Weintraub A, Allshouse A, Morey C, Cusick C, et al. (2008) A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. J Head Trauma Rehabil 23: 52-63.