

Understanding the neurotransmitter changes underlying cognitive dysfunction in traumatic brain injury and possible therapeutic targets: a review

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Traumatic brain injury (TBI) is the primary cause of death and disability in younger individuals [1]. To date, the mechanism behind the cognitive dysfunction following TBI remains unclear. Neurotransmitters (NT) represent a particularly important system in physiological events relevant to cognition affected by TBI [2]. Preclinical evaluations of both agonists and antagonists affecting acetylcholine (ACh) and the dopamine (DA) system have shown marked benefits for cognitive recovery.

Hence, the aim of this article is to outline clinical studies that have shown potential efficacy of ACh- and DA-oriented medications in the treatment of TBI.

PubMed was used to search for articles published since 1998 that reported any association between cognitive dysfunction following TBI. Before 1998, no clinical studies regarding the neurotransmitter-targeted therapies in TBI had been reported. After reviewing the abstracts, 14 articles were submitted to the final evidence review.

Acetylcholinesterase (AChE) inhibitors are most beneficial for the treatment of posttraumatic cognitive impairments [3]. Principally, rivastigmine improved the cognitive function in TBI patients [4]. However, the results from randomized controlled trials have remained modest [5]. Zhang *et al.* [6] performed a 24-week, randomized, placebo-controlled, double-blind crossover trial to demonstrate sustained improvements in immediate auditory and visual memory, attention, working memory and information processing speed. An open-label study conducted by Tenovuo [7] also found a subjective and longer (average 24 months) improvement following donepezil (summarized in Table I).

Dopamine represents a unique role in the NT system within the central nervous system (CNS) due to its influences on a number of physiologic functions including working memory, behavioral flexibility, and decision making [8].

In 2006, the Neurotrauma Foundation (NTF) recommended three drugs with DAergic effects to be used in TBI patients to enhance cognitive recovery and rehabilitation [9]. The identified drugs were methylphenidate (MPD), amantadine hydrochloride (AMH), and bromocriptine [9].

Multiple studies have demonstrated the effectiveness of MPD used in TBI patients with cognitive dysfunction especially in information processing speed [10], attention [11, 12], alertness [13], and working mem-

Table I. Acetylcholinesterase inhibitors for cognitive rehabilitation after TBI

Study	Design	Participants	Interventions	Primary outcomes	Notes
Silver <i>et al.</i>	26-week double-blind open-label	134 adults with TBI	12 mg daily of rivastigmine	Verbal learning test visual information processing	An extension study
Tenuvuo <i>et al.</i>	8-week	69 patients with TBI	12 mg daily rivastigmine	Computerized neuropsychological testing and standardized clinical interviews	A weak trend favoring rivastigmine was observed
Zhang <i>et al.</i>	RCT crossover, double blind	18 participants with mild-severe TBI	5–10 mg/day of donepezil	*All, VII PASAT	
Tenovuo <i>et al.</i>	Retrospective pseudo-randomized cohort	111 patients with mild to moderate TBI	5 mg/day of donepezil 4 mg/day of galantamine 1.5 mg/day of rivastigmine	Self-assessment rated from no response to excellent response	No differences were found among the three drugs

*All indicates Auditory Immediate Index, VII – Visual Immediate Index, PASAT – Paced Auditory Serial Addition Test.

Table II. Dopamine drugs for cognitive rehabilitation after TBI

Study	Design	Participants	Interventions	Primary outcomes	Notes
Whyte <i>et al.</i>	6-week double-blind placebo-controlled repeated crossover study	34 adults with moderate to severe TBI and attention complaints	0.3 mg/kg dose MPD, twice a day	Processing speed Work attentiveness Caregiver rating of attention Reaction time	
Pavlovskaya <i>et al.</i>	4-week	6 patients with severe TBI	5–10 mg/day of MPD	Author-modified Attention based performance	No objective assessment
Willmott <i>et al.</i>	RCT, crossover, double blind	40 participants with moderate-severe TBI	0.3 mg/kg twice daily of MPD	Processing speed Selective attention task Dissimilar compatible	
Lee <i>et al.</i>	4 week double-blind parallel-group trial	30 patients with mild to moderate TBI	5–20 mg/day of MPD	MMSE	
Kim <i>et al.</i>	Double-blind placebo-controlled study	18 subjects with TBI	20 mg/day of MPD	Working memory and visuospatial attention tasks	
Kraus <i>et al.</i>	An open-label design	Twenty-two subjects with TBI	400 mg/day of AMH	Neuropsychological test Executive function	
Patrick <i>et al.</i>	A retrospective review	10 children with severe TBI and a low response state	100–400 mg/day of AMH	Arousal/attention and auditory response Expressive communication visual response Tactile response and olfactory response	
Ben <i>et al.</i>	Case report	An old patient with severe TBI associated with PD	AMH (unknown dose)	Author modified tests Motor function and cognitive function	
McDowell <i>et al.</i>	RCT cross over	24 patients with severe TBI	1 dose of bromocriptine	Executive function	No effect on the working memory Related to prefrontal function
McAllister <i>et al.</i>	Unblinded controlled study	26 individuals with mild TBI	1.25 mg bromocriptine	A neuropsychological test battery	

ory [14] after brain trauma. However, there is no longer than six months follow-up in the clinical trials regarding MPD in patients with TBI.

Amantadine hydrochloride has also been found to be effective at treating cognitive dysfunction post-TBI in both clinical trials and case reports. Kraus *et al.* [15] showed that AMH treatment improved prefrontal executive function in TBI patients correlated with an increase in left prefrontal cortex glucose metabolism. Patrick *et al.* [16] reported that AMH accelerated recovery of attention deficit in children with a lower response following brain injury.

Bromocriptine is a specific D2 receptor agonist, and a past case report [17] showed improvements in motor function and executive function after administering bromocriptine in a severe TBI patient associated with Parkinson's syndrome. In contrast, McDowell *et al.* did not find that bromocriptine appeared to improve attentional difficulties in moderate to severe TBI patients. However, this study employed a relatively high dose of bromocriptine at 10 mg/day for a more prolonged treatment period than previously studied in TBI [18]. In addition, a 6-week placebo-controlled pilot study showed that bromocriptine in TBI patients also did not enhance attentional skills [19] (summarized in Table II).

This brief review has sought to summarize the evidence that supports an NT-oriented hypothesis of cognitive dysfunction after TBI and provide a context for the use of Ach and DA targeted therapies during patient rehabilitation.

In conclusion, it seems that applications of AChE inhibitors and DA agonists are beneficial in TBI patients with cognitive dysfunction.

Conflict of interest

The authors declare no conflict of interest.

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