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Review

# 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptor agonists: A decade of empirical evidence supports their use as an efficacious therapeutic strategy for brain trauma

*Jeffrey P. Cheng*[a,b], *Jacob B. Leary*[a,b,1], *Aerin Sembhi*[a], *Clarice M. Edwards*[a,b], *Corina O. Bondi*[a,b,e], *Anthony E. Kline*[a,b,c,d,e,f,*]

[a]*Physical Medicine & Rehabilitation, University of Pittsburgh, Pittsburgh, PA 15213, United States*
[b]*Safar Center for Resuscitation Research, University of Pittsburgh, Pittsburgh, PA 15213, United States*
[c]*Psychology, University of Pittsburgh, Pittsburgh, PA 15213, United States*
[d]*Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA 15213, United States*
[e]*Center for Neuroscience, University of Pittsburgh 1letab, Pittsburgh, PA 15213, United States*
[f]*Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA 15213, United States*

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ABSTRACT

Traumatic brain injury (TBI) is a significant and enduring health care issue with limited treatment options. While several pre-clinical therapeutic approaches have led to enhanced motor and/or cognitive performance, the benefits of these treatments have not translated to the clinic. One plausible explanation is that the therapies may not have been rigorously evaluated, thus rendering the bench-to-bedside leap premature and subsequently unsuccessful. An approach that has undergone considerable empirical research after TBI is pharmacological targeting of 5-HT$_{1A}$ receptors with agonists such as repinotan HCl, 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), and buspirone. The goal of this review is to integrate and interpret the findings from a series of studies that evaluated the efficacy of 5-HT$_{1A}$ receptor agonists on functional, histological, and molecular outcome after acquired brain injury. The overwhelming consensus of this exhaustive review is that a decade of empirical evidence supports their use as an efficacious therapeutic strategy for brain trauma.

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*Correspondence to: Departments of Physical Medicine & Rehabilitation, Critical Care Medicine and Psychology, University of Pittsburgh, 3471 Fifth Ave., Suite 201, Pittsburgh, PA 15213, United States. Fax: +412 624 0943.
E-mail address: klineae@upmc.edu (A.E. Kline).
[1]Current address: Rehabilitation Medicine Department, Clinical Center, NIH, Bethesda, MD 20892.

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## Contents



## 1. Introduction

Traumatic brain injury (TBI) affects an estimated 10 million people worldwide (Hyder et al., 2007). Many suffer significant neurological disabilities (Max et al., 1991; Sosin et al., 1995; Thurman et al., 1999; Langlois et al., 2004; Selassie et al., 2008; Faul et al., 2010) that preclude their ability to remain self-sufficient. Moreover, the financial burden resulting from medical and rehabilitative care as well as diminished productivity is estimated to be greater than $76.5 billion per year (Langlois et al., 2004; Faul et al., 2010). Accordingly, if individuals who sustain a TBI are to once again become integrated and productive members of society, the identification, refinement, and effective implementation of treatment strategies capable of producing neurobehavioral and cognitive recovery after TBI is essential.

Numerous therapeutic approaches have been conducted after experimental TBI and many of them have shown significant improvement in locomotor and cognitive performance, as well as decreases in histological damage (see excellent reviews by Kokiko and Hamm, 2007; Bales et al., 2009; Wheaton et al., 2009; Garcia et al., 2011). However, these interventions have not translated to the clinic (Doppenberg et al., 2004; Menon, 2009). One plausible explanation is that the therapies may not have been rigorously evaluated at the bench, thus rendering the bench-to-bedside leap premature and consequently unsuccessful. An approach that has undergone considerable empirical research after TBI is pharmacological targeting of 5-$HT_{1A}$ receptors with agonists such as repinotan HCl, 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), and buspirone.

5-$HT_{1A}$ receptors are the most studied and best-characterized of the fourteen 5-HT receptor subtypes (Barnes and Sharp, 1999). They are abundantly expressed in key brain regions that subserve learning and memory, such as the cortex and hippocampus, and thus play a prominent role in cognition (Barnes and Sharp, 1999; Meneses 1999; Meneses and Perez-Garcia, 2007). 5-$HT_{1A}$ receptors are also susceptible to neuronal damage induced by TBI or other CNS injuries (De Vry et al., 1997, 1998) and thus it is plausible that these receptors could be an important and potentially efficacious therapeutic target to investigate after TBI. Indeed, the limited, albeit, persuasive studies in this comprehensive review show that manipulating this system confers significant cognitive and histological benefits after brain trauma.

The primary objective of this review is to integrate the current literature based on experiential studies evaluating 5-$HT_{1A}$ receptor agonists for their effect on cognitive, motor, histological and/or molecular outcome after brain trauma. The secondary goal is to invigorate interest in this still understudied, but efficacious therapeutic approach for TBI. The importance of evaluating therapies that act on the 5-HT neurotransmitter system is that to date only the partial dopamine$_2$ ($D_2$) receptor agonist amantadine has shown some promise translating from bench-to-bedside when administered in the sub-acute phase after severe TBI (Giacino et al., 2012). Clearly, additional research is necessary to discover potential pharmacotherapies that may treat the debilitating consequences of TBI. As this comprehensive review shows, a decade of experiential evidence supports the use of 5-$HT_{1A}$ receptor agonists as an efficacious therapeutic strategy for brain injury.

Using the specific key-terms “traumatic brain injury” AND “serotonin $_{1A}$” 27 articles were identified by PubMed. Refining the search to “traumatic brain injury” AND “5-$HT_{1A}$ receptor agonists”, yielded 17 articles of which 7 were specific to TBI. The same terms in Scopus returned 23 and 13 articles, respectively, with 13 specific to TBI (including the 7 from PubMed). Finally, after reviewing the bibliographies of the papers that were exclusive to TBI, an additional 2 papers were identified that fit the criteria of brain trauma, albeit not “traumatic” per se. These 2 papers focused on acute subdural hematomas (ASDH) and were included because hematomas are the most common mass lesions after TBI (Alessandri et al., 1999). Hence, the review focuses on 15 papers, of which 14 are experimental and 1 is clinical. All studies are described in the body and briefly summarized in Table 1.