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Review article

Combination therapies for neurobehavioral and cognitive recovery after experimental traumatic brain injury: Is more better?

Anthony E. Kline[a,b,d,e,f,g,*], Jacob B. Leary[a,b,1], Hannah L. Radabaugh[a,b], Jeffrey P. Cheng[a,b], Corina O. Bondi[a,b,c]

[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] Neurobiology, University of Pittsburgh, Pittsburgh, PA 15213, United States
[d] Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA 15213, United States, United States
[e] Psychology, University of Pittsburgh, Pittsburgh, PA 15213, United States
[f] Center for Neuroscience, University of Pittsburgh, Pittsburgh, PA 15213, United States
[g] 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 health care crisis that affects two million individuals in the United Sates alone and over ten million worldwide each year. While numerous monotherapies have been evaluated and shown to be beneficial at the bench, similar results have not translated to the clinic. One reason for the lack of successful translation may be due to the fact that TBI is a heterogeneous disease that affects multiple mechanisms, thus requiring a therapeutic approach that can act on complementary, rather than single, targets. Hence, the use of combination therapies (i.e., polytherapy) has emerged as a viable approach. Stringent criteria, such as verification of each individual treatment plus the combination, a focus on behavioral outcome, and post-injury vs. pre-injury treatments, were employed to determine which studies were appropriate for review. The selection process resulted in 37 papers that fit the specifications. The review, which is the first to comprehensively assess the effects of combination therapies on behavioral outcomes after TBI, encompasses five broad categories (inflammation, oxidative stress, neurotransmitter dysregulation, neurotrophins, and stem cells, with and without rehabilitative therapies). Overall, the findings suggest that combination therapies can be more beneficial than monotherapies as indicated by 46% of the studies exhibiting an additive or synergistic positive effect versus on 19% reporting a negative interaction. These encouraging findings serve as an impetus for continued combination studies after TBI and ultimately for the development of successful clinically relevant therapies.

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Abbreviations: AdGDNF, adenoviral glial cell line-derived neurotrophic factor; adgdn, blood brain barrier; BDNF, brain derived neurotrophic factor; bFGF, basic fibroblast growth factor; BrdU, bromdeoxyuridine; CBF, cerebral blood flow; CCI, controlled cortical impact; DHA, docosahexaenoic acid; EE, environmental enrichment; EPO, erythropoietin; eSCs, embryonic stem cells; FGF-2, fibroblast growth factor-2; FP, fluid percussion; G-CSF, granulocyte-colony stimulating factor; HAL, haloperidol; hUCBCs, human umbilical cord blood cells; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin - 1β; IL-10, interleukin-10; $MgCl_2$, magnesium chloride; MPH, methylphenidate; MINO, minocycline; NAC, *N*-acetylcysteine; NAM, nicotinamide; NGF, nerve growth factor; RNS, reactive nitrogen species; ROS, reactive oxygen species; STD, standard; TBI, traumatic brain injury; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; 4-HHE, 4-hydroxy-2-hexenal; 4-HNE, 4-hydroxy-2-nonenal; 5-HT_{1A}, serotonin$_{1A}$; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino) tetralin; VEGF, vascular endothelial growth factor.

* Corresponding author at: Department of Physical Medicine & Rehabilitation and Safar Center for Resuscitation Research, University of Pittsburgh, 3471 Fifth Ave., Suite 201, Pittsburgh, PA 15213, United States.
E-mail address: klineae@upmc.edu (A.E. Kline).
[1] Current affiliation: Rehabilitation Medicine Department, Clinical Center, National Institutes of Health, MSC 1604, Bethesda, MD 20892, United States.

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1. Introduction

With an estimated incidence of two million cases in the United States each year (Faul et al., 2010; Albrecht et al., 2015), and several million more worldwide (Hyder et al., 2007), traumatic brain injury (TBI) is a significant health care issue (Max et al., 1991; Thurman and Guerrero, 1999; Hyder et al., 2007; Summers et al., 2009; Coronado et al., 2011). Motor vehicle accidents and falls resulting in a blow to the head are the typical causes of TBI in the general population, whereas blasts and shrapnel from improvised explosive devices are the leading causes for military personnel in active war zones (Ling et al., 2009; Cernak and Noble-Haeusslein, 2010; Young et al., 2015). Brain traumas range from mild to severe with the former being the case in the majority of occurrences (Sosin et al., 1996) and generally not displaying marked behavioral symptoms, while the latter occurs less often, but presents significant motor and/or cognitive dysfunction that can have perpetual adverse consequences on the quality of life (Binder, 1986; Millis et al., 2001). TBI can also increase the risk for other neurological disorders such as seizures (D'Ambrosio et al., 2004; D'Ambrosio and Perucca, 2004; Curia et al., 2011), Alzheimer's disease (Sullivan et al., 1987; Schofield et al., 1997; Fleminger et al., 2003; Ikonomovic et al., 2004; DeKosky et al., 2007; Gupta and Sen, 2016; Scott et al., 2016) and Parkinson's disease (Goldman et al.,