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Review

# Catecholaminergic based therapies for functional recovery after TBI

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ABSTRACT

Among the many pathophysiologic consequences of traumatic brain injury are changes in catecholamines, including dopamine, epinephrine, and norepinephrine. In the context of TBI, dopamine is the one most extensively studied, though some research exploring epinephrine and norepinephrine have also been published. The purpose of this review is to summarize the evidence surrounding use of drugs that target the catecholaminergic system on pathophysiological and functional outcomes of TBI using published evidence from pre-clinical and clinical brain injury studies. Evidence of the effects of specific drugs that target catecholamines as agonists or antagonists will be discussed. Taken together, available evidence suggests that therapies targeting the catecholaminergic system may attenuate functional deficits after TBI. Notably, it is fairly common for TBI patients to be treated with catecholamine agonists for either physiological symptoms of TBI (e.g. altered cerebral perfusion pressures) or a co-occuring condition (e.g. shock), or cognitive symptoms (e.g. attentional and arousal deficits). Previous clinical trials are limited by methodological limitations, failure to replicate findings, challenges translating therapies to clinical practice, the complexity or lack of specificity of catecholamine receptors, as well as potentially counfounding effects of personal and genetic factors. Overall, there is a need for additional research evidence, along with a need for systematic dissemination of important study details and results as outlined in the common data elements published by the National Institute of Neurological Diseases and Stroke. Ultimately, a better understanding of catecholamines in the context of TBI may lead to therapeutic advancements.

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## Contents



## 1. Introduction

Traumatic Brain Injury (TBI) is a significant public health problem in the United States. In 2010 alone, an estimated 2.5 million TBI cases presented for treatment and it is likely that many more cases went unreported (Centers for Disease Control and Prevention, 2015). The mechanism of injury varies greatly and includes motor vehicle accidents, falls, and gunshot wounds, to name a few; the unpredicatable nature of TBI complicates the establishment of preventative measures. Thus it is imperative to identify effective treatments that prevent secondary injury (NIH, 1998). While TBI has become a largely survivable condition, an estimated 50% of TBI survivors live with long-term functional deficits (Kraus et al., 2005; Thurman et al., 1999). Post-TBI, deficits are common in several functional domains, including: learning (e.g. information processing), memory (short- and long-term), executive function (e.g. problem solving; impulse control) and/or other areas (e.g. language; attention; agitation; mood/affect) (Arciniegas et al., 2000; Dyer et al., 2006; Oddy et al., 1985; Sun and Feng, 2013). TBI survivors have elevated rates of mental health symptoms including: depression (Jorge et al., 2004; Moldover et al., 2004; Seel et al., 2003), agitation (Bogner et al., 2015), impulsivity, and verbally aggressive behavior (Dyer et al., 2006). Cognitive, behavioral, and mood symptoms are distressing and challenging to cope with. These symptoms may also impair the survivor's ability to return to pre-injury roles (e.g. work, family, social) and contribute to caregiver burden (Binder, 1986).

Though changes in behavior may occur without measurable changes in physiology, the aforementioned TBI long-term deficits are often accompanied by changes in key brain structures known to control the functions affected, including the hippocampus, thalamus, and frontal cortex (Bramlett and Dietrich, 2002; Lifshitz et al., 2007; Vertes, 2006). Beyond the brain structures themselves, there are post-TBI alterations in brain cell communication via changes in underlying neurotransmitter systems; pathologic changes in these systems represent potential therapeutic targets for novel TBI therapies. The focus of this invited review is limited to one family of neurotransmitters: the catecholaminergic system. Catacholamines neurotransmitters fall into the monoamine family, which are derived from aromatic amino acids (e.g. L-tyrosine) and have a characteristic structure comprised of an amino group connected to a ring by a short double carbon chain. Catecholamines bind to adrenergic receptors (e.g. α β), which are found throughout the body. This system is known to be altered following TBI; an acute catecholamine surge can be detected in the form of increased plasma levels (Hamill et al., 1987; Tran et al., 2008; Woolf et al., 1987). Moreover, there are commercially available drugs that target these neurotransmitters either directly or indirectly. In fact, some catecholamines (e.g. norepinephrine; dopamine) are commonly administered vasopressors used to raise cerebral perfusion pressure (CPP) and mean arterial blood pressure (MAP) after TBI; use of catecholamines has been associated with clinically-relevant increases in CPPs that varied depending on which catecholamine was given in studies of pediatric- (Di Gennaro et al., 2011) and adult- (Sookplung et al., 2011) TBI. There is also clinical evidence associating use of norepinephrine- and dopamine- agonist stimulants with less severe agitation after TBI (Bogner et al., 2015). Despite the association between catecholamine therapy outcomes, relatively little causal evidence exists and what has been