Review

Not peer-reviewed version

Multi-mechanistic Approaches to the Treatment of Traumatic Brain Injury: A Review

Daniel G Lynch , Raj K Narayan , Chunyan Li *

Posted Date: 27 February 2023

doi: 10.20944/preprints202302.0471.v1

Keywords: Traumatic brain injury; Combination therapy; Multimodal therapy; Multimodal neuromonitoring; Pharmacologic; Non-pharmacologic

Review

Multi-Mechanistic Approaches to the Treatment of Traumatic Brain Injury: A Review

Daniel G Lynch [1,2], Raj K Narayan [1,3] and Chunyan Li [1,2,4,*]

[1] Translational Brain Research Laboratory, The Feinstein Institutes for Medical Research, Manhasset, NY 11030, USA
[2] Zucker School of Medicine at Hofstra/Northwell Health, Hempstead NY 11030, USA
[3] Department of Neurosurgery, St. Francis Hospital, Roslyn, NY 11576, USA
[4] Department of Neurosurgery, Northwell Health, Manhasset, NY 11030, USA
* Correspondence: CLi11@northwell.edu

Abstract: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. Despite extensive research efforts, the majority of trialed monotherapies to date have failed to demonstrate significant benefit. It has been suggested that this is due to the complex pathophysiology of TBI, which may possibly be addressed by a combination of therapeutic interventions. In this article, we have reviewed combinations of different pharmacologic treatments, combinations of non-pharmacologic interventions, and combined pharmacologic and non-pharmacologic interventions for TBI. Both preclinical and clinical studies have been included. While promising results have been found in animal models, clinical trials of combination therapies have not yet shown clear benefit. This may possibly be due to their application without consideration of the evolving pathophysiology of TBI. Improvements of this paradigm may come from novel interventions guided by multimodal neuromonitoring and multimodal imaging techniques, as well as the application of multi-targeted non-pharmacologic and endogenous therapies. There also needs to be a greater representation of female subjects in preclinical and clinical studies.

Keywords: traumatic brain injury; combination therapy; multimodal therapy; multimodal neuromonitoring; pharmacologic; non-pharmacologic

1. Introduction

Traumatic brain injury (TBI) is a major global contributor to disability and death [1]. Central nervous system (CNS) damage induced by TBI is characterized by the initial primary injury with focal and diffuse tissue damage followed by secondary injury due to multiple pathophysiologic cascades including neuroinflammation, ischemia, oxidative stress, excitotoxicity and cerebral edema [1–3]. In spite of decades of fairly concerted efforts to minimize these secondary processes following TBI, there has been a history of promising results in preclinical studies that fail to show benefit in clinical trials [4]. To explain this failure, it has been suggested that TBI is not a homogenous disease state but rather a syndrome including a wide range of pathophysiologic derangements that undergo a complex and dynamic evolution over time [4]. Recognizing this, the National Institute of Neurologic Disorders and Stroke (NINDS) has since 2008 recommended research into combination therapies including multiple different pharmacologic and/or non-pharmacologic interventions to better address the multifactorial pathophysiology of TBI [5]. While initially promising, combination therapies for TBI have had mixed outcomes with some studies demonstrating benefit and others failing to show significant benefit compared to individual treatments [6]. It has been proposed that failure to take into account the evolution of secondary injury mechanisms over time may have led to the mixed results seen in initial trials of combination therapies [7]. For example, the cellular and molecular drivers of oxidative stress are different in the initial minutes after TBI as compared to over the subsequent hours and days [8]. Researchers have suggested that an ideal treatment plan would not just administer a combination of therapies with different mechanistic targets, but also take into

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2023 doi:10.20944/preprints202302.0471.v1

account how the evolution of secondary injury pathophysiology may play a different role at various time-points [7].

In the interests of clarity, it should be noted that following TBI, especially when severe, there are many secondary insults that may worsen the ultimate outcome. These include hypotension, hypoxia, seizures, hematoma expansion, brain edema, elevated intracranial pressure and fever, among others [2,4]. In the past few decades, the proliferation of Neuro ICUs and Neuro Critical Care as a specialty acknowledges the recognition of these secondary insults and aims to prevent them, or to treat them expeditiously [9]. These secondary insults should not be confused with the secondary pathophysiological processes described earlier which constitute the focus of this review.

The need for integrated multitargeted treatments for TBI has been recognized [7], however studies of such treatments are rare in the preclinical and clinical literature. The current state of multitarget treatment research has remained largely unchanged since NINDS first recommended investigation of combination therapies [5], consisting of combinations of treatments individually shown to be effective in prior single-target trials without necessarily considering the temporal evolution of TBI [6]. While such an approach has been proposed as a logical refinement of combination treatments [7], to date few if any trials have attempted this complex treatment protocol. However there exists a large body of trials investigating combination therapies that, in conjunction with an understanding of the drivers of secondary injury, may allow for the creation of integrated multitarget treatment protocols. This review therefore seeks to summarize the progress that has been made on combination therapeutic interventions in the nearly 15 years since they were first recommended by NINDS, as well as highlight the utility of multimodal neuromonitoring and multimodal imaging to guide treatment regimens. In addition, current and ongoing work relating to multimodal treatment is discussed, with an emphasis on the integration of non-pharmacologic treatments and endogenous mechanisms.

2. Materials and Methods

2.1. Eligibility Criteria

A review of the available literature was conducted, selecting articles published up to December of 2022. The inclusion criteria were: (1.) Preclinical or clinical studies of TBI; including mild, moderate, and severe TBI in both adult and pediatric populations. (2.) Studies investigating combinations of pharmacologic and/or non-pharmacologic interventions or investigating multiple multimodal neuromonitoring parameters used to guide treatment of TBI. Exclusion criteria included articles not published in English, abstracts, book chapters and articles that could not be accessed for full-text review. Previous review articles were excluded from analysis, but studies cited within reviews were examined for eligibility.

2.2. Literature Search

The MedlinePlus and Cochrane databases were searched for relevant articles. Pharmacologic interventions were similarly searched using “traumatic brain injury” AND “pharmacologic” OR “multimodal pharmacologic” OR “combination pharmacologic” (352 results). Articles investigating non-pharmacologic interventions were found with the keywords “traumatic brain injury” AND “non-pharmacologic treatment” OR “non-pharmacologic therapy” (259 results). The search string “traumatic brain injury” AND “combination therapy” OR “combination treatment” OR “multimodal treatment” OR “multimodal therapy” with keywords limited to title or abstract was used to identify any articles that may have escaped initial screening (2,983 results). Articles investigating multimodal neuromonitoring as applied to TBI treatment were identified using “traumatic brain injury” AND “multimodal monitoring” OR “multimodal neuromonitoring” AND “treatment” (192 results). Articles were selected for inclusion based on title and abstract screening by an author (DGL).

2.3. Study Selection

After screening for articles that met inclusion criteria and adding articles missed on initial search, 208 potentially relevant articles on pharmacologic interventions and 170 articles investigating non-pharmacologic interventions were identified, along with 338 articles relating to multimodal neuromonitoring (MMM). After full text screening, 42 articles investigating combinations of pharmacologic interventions (Table 1) and 5 articles investigating non-pharmacologic interventions (Table 2) were selected for analysis. Additionally, 13 articles were identified as including combinations of pharmacologic and non-pharmacologic interventions and extracted into a separate category (Table 3). After review, 12 relevant MMM-related articles were found that met selection criteria (Table 4).

3. Results

3.1. Multi-mechanistic Pharmacologic Interventions

TBI is a complex and heterogeneous disease process, and the secondary processes that follow TBI include oxidative stress, excitotoxicity, inflammation, neuronal loss and glial cell activation. Given this wide variety of underlying drivers of secondary damage, multitargeted medications have been trialed to address the pathophysiology of TBI on multiple fronts [10]. However, these multitargeted interventions have to date largely been unsuccessful in clinical trials [5]. As the pathophysiology of secondary injury evolves over time, theraputic interventions must be able to adapt to the evolution in molecular causes of injury; each medication is likely to have a unique theraputic time window or windows based on the molecular timeline of secondary injury, during which it is most effective and outside of which it may lack significant benefit [11]. It should be noted that many interventions target secondary insults that occur after TBI (tissue ischemia, edema, hypotension, etc.) rather than the pathophysiologic mechanisms underlying these changes [2,12] which must be taken into account when comparing experimental protocols.

Following full-text review, 42 articles were identified as investigating a pharmacologic treatment strategy employing combinations of medications to treat preclinical or clinical TBI (Table 1). A diverse range of pharmacologic interventions were identified, including antioxidants, anti-convulsants, anti-excitatory and anti-inflammatory compounds. Multiple interventions from different classes were typically applied in combination, to take advantage of synergistic mechanisms of action. The majority of trials (39/42) were in a preclinical animal model, with only 3 clinical studies.

Table 1. Pharmacologic interventions trialed for TBI treatment.

Model	Population	Sample Size	%Fem	Intervention	Outcome of Combination Therapy	Reference
				Clinical Trials		
Case Series	Severe Human TBI	2	0%	Cerebrolysin, citicoline	Improved long-term neurologic recovery with combined therapy in acute TBI	Trimmel, 2022
Retrospective Observational	Severe Human TBI	117	20.6%	HTS, mannitol, barbiturates, propofol, fentanyl	Propofol & fentanyl reduced ICP, but less than HTS in patients with acute TBI	Colton, 2014
Randomized Placebo Controlled	Severe Human TBI	14	21.4%	Probenecid, NAC	No harmful effects from combo in Phase I trial in acute pediatric TBI	Clark, 2017
				Preclinical Trials		

CCI	Mouse	36	0%	NSC, olfactory ensheathing cells, valproic acid	Improved behavioral function and NSC neuronal differentiation	Liu, 2022
CCI	Mouse	292	45.9%	Apocynin, salubrinal, TBHQ	Improved functional outcomes, brain lesion development and reduced inflammation	Davis, 2022
Biopsy Punch	Rat	45	0%	NSC, curcumin nanoparticles	Reduced glial activation & edema, improved recovery	Narouiepour, 2022
CHI	Mouse	26	0%	Minocycline, NAC	Improved memory function and reduced neuronal loss	Whitney, 2021
CCI	Mouse	10	0%	Apocynin, TBHQ	Reduced white matter disruption	Chandran, 2021
Weight Drop	Mouse	44	0%	Ketamine, perampanel	Reduced neurobehavioral dysfunction and NF-kB/iNOS expression	Alqahtani, 2020
Weight Drop	Rat	32	0%	Felbamate, levetiracetam	Reduced pro-inflammatory cytokines and histologic damage	Bayhan, 2020
Weight Drop	Rat	42	0%	Doxycycline, tocopherol	Reduced neurobehavioral deficits, ROS and pro-inflammatory cytokines	Rana, 2020
Weight Drop	Rat	30	0%	MDL28170, BMSC	Reduced inflammation and improved survival of stem cells, with reduced neurobehavioral impairment	Hu, 2019
Weight Drop	Rat	24	100%	Lomerizine, YM872, Brilliant Blue G	Decreased microglial activation and myelin disruption without affecting neurobehavioral impairment	Mao, 2018
CCI	Mouse	NR	0%	Minocycline, NAC	Prevented loss of oligodendrocytes following CCI	Sangobowale, 2018
CCI	Rat	24	0%	Magnesium, NAT	Reduced BBB disruption and improved functional outcomes	Ameliorate, 2017
CCI	Mouse	31	0%	DHA, NSC	Improved neurogenesis and functional outcomes, with increased astrocyte and microglia activation	Ghazale, 2018
CCI	Mouse	NR	0%	Apocynin, TBHQ	Improved function and lesion volume	Chandran, 2018
mCCI	Rat	NR	0%	Minocycline, NAC	Protected oligodendrocytes and increased M1/M2 microglial activation	Haber, 2018
FPI	Rat	70	0%	Memantine, estradiol	Improved functional deficits and reduced neuronal degeneration	Day, 2017

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2023 doi:10.20944/preprints202302.0471.v1

CCI	Rat	96	0%	Magnesium, PEG	Improved CNS penetration of magnesium, increased neuroprotection	Busingye, 2016
CCI	Rat	207	0%	BMSC, propranolol	Decreased long term neurobehavioral deficits	Kota, 2016
CHI	Rat	35	0%	Carnosine, Cyclosporine	Decreased pro-inflammatory cytokines and neuronal apoptosis	Baky, 2016
In-Vitro TBI	Rat Brain Slices	NR	0%	Memantine, estradiol	Reduced neuronal death	Lamprecht, 2015
Cryo-Injury	Mouse	70	0%	BMDC, lipoic acid	Increased cell growth in perilesional penumbra, decreased astrocyte infiltration, increased microglial activation	Paradells, 2015
CCI	Rat	40	0%	Progesterone, vitamin D	Reduced neuronal loss and astrocyte activation, mediated through downregulations in TLR4/NF-kB	Tang, 2015
CCI	Rat	31	0%	G-CSF, hUCB	Reduced activation of microglia and improved neurogenesis and functional recovery	Acosta, 2014
CCI	Rat	40	0%	Etanercept, lithium	Reduced edema and neuronal/glial apoptosis	Ekici, 2014
mCCI	Rat	NR	NR	Minocycline, NAC	Reduced neuroinflammation and neurobehavioral deficits	Haber, 2013
CCI	Mouse	126	0%	Lithium, valproic acid	Reduced BBB disruption, lesion volume, neuronal degeneration and functional deficits	Yu, 2013
CCI	Rat	74	NR	Progesterone, magnesium	Reduced neuronal apoptosis and neurobehavioral deficits	Uysal, 2013
CCI	Mouse	50	0%	Melatonin, dexamethasone	Reduced lesion volume, oxidative stress and functional deficits	Campolo, 2013
CCI	Mouse	44	0%	Dexamethasone, bortezomib	Reduced edema and BBB disruption	Thal, 2013
CCI	Rat	128	0%	Progesterone, vitamin D	Reduced neuronal loss and astrocyte activation	Tang, 2013
CCI	Rat	38	0%	Nimodipine, melatonin	Worsened edema and neuronal necrosis compared to melatonin alone	Ismailoglu, 2012
CCI	Rat	46	0%	Progesterone, vitamin D	Improved neurobehavioral function and increased astrocyte activation	Hua, 2012
CHI	Mouse	39	0%	VEGF, FGF2	Improved functional outcomes, no additional benefit versus monotherapy	Thau-Zuchman, 2012

CHI	Rat	35	100%	Estrogen, progesterone	Less reduction of edema and anti-inflammatory cytokines versus estrogen alone	Khaksari, 2011
CCI	Rat	50	0%	Minocycline, melatonin	No significant effect	Kelso, 2012
CHI	Rat	32	0%	Magnesium, MK801	Reduced edema and BBB disruption, but no greater effect than monotherapy	Imer, 2009
CCI	Rat	NR	NR	L-arginine, D-arginine, SOD, catalase	Increased nitric oxide and cerebral blood flow after TBI	Cherian, 2003
mCCI	Rat	30	0%	MK801, scopolamine	Improved hippocampal neuronal death and associated memory deficits	Jenkins, 1999
FPI	Rat	42	NR	Morphine, scopolamine	Improved functional outcomes	Lyeth, 1993

3.1.1. Antioxidant Treatments

Oxidative stress begins in the hyperacute phase, within seconds of TBI, due to disruptions in blood flow and hypoxia that induce metabolic supply-demand mismatch in neurons, leading to activation of NADPH oxidase (NOX) [13]. NOX generates reactive oxygen species (ROS) and reactive nitrogen species (RNS) that contribue to DNA damage, mitochondrial dysfunction and neuronal death, with the initial peak of NOX activity occuring in neurons approximately one hour after TBI, and a secondary microglia-mediated peak of NOX activity 24-96 hours after TBI [13]. ROS and RNS also cause the peroxidation of lipids and proteins, disrupting the function of surviving cells and impairing the normal anti-oxidative response [8,14]. In a healthy brain, oxidative stress leads to induction of antioxidant enxymes including superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT) [8], however this response can be blunted in TBI [15]. Moving beyond the subacute period, oxidative stress and cell damage contributes to the chronic neurinflammatory and neurodegenerative sequelae of TBI [8,14].

Antioxidant therapies including free radical scavengers, antioxidant enzymes and activators of endogenous antioxidant systems have been trialed in TBI [8]. N-acetylcysteine (NAC) is a precursor to glutathione, an endogenous free radical scavenger that is known to be depleted in the subacute phase of TBI [8]. There is a lack of multimodal clinical trials of antioxidant therapies involving NAC, however, in a phase I randomized trial, NAC in combination with probenecid had no observed harmful effects, which may support future phase II and III clinical trials of similar antioxidant combinations [16]. L-arginine is a vasoactive amino acid which has been found to be depleted within hours of TBI, and low l-arginine levels are associated with increased RNS generation [17].

In preclinical models, a combination of arginine and antioxidant enzymes (CAT, SOD) has been used to modulate ROS generation and cerebral blood flow following TBI [18]. Some groups have begun to investigate novel multimodal pharmacologic interventions to better address the pathophysiology of TBI. A combination therapy including apocynin, tert-butylhydroquinone (tBHQ) and salubrinal was trialed in a preclinical model of TBI to target multifactorial causes of cellular stress [19]. Apocynin inhibits NOX, [20], while tBHQ upregulates genes encoding anti-oxidant enzymes [21,22] and salubrinal helps to reduce the production of misfolded proteins following TBI, preventing cell stress associated with accumulation of nonfunctional proteins [23], and has also been shown to reduce activation of pro-inflammatory cellular pathways [24]. This combination was found to improve lesion volume and improved functional outcomes after TBI, and this triple combination therapy had better outcomes compared to animals treated with only apocynin and tBHQ [19]. The authors also found these effects to be associated with reductions in activated microglia and peripheral immune cells in the peri-contusional cortex, along with decreased oxidative DNA damage. While

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2023 doi:10.20944/preprints202302.0471.v1

these results must be replicated in large animal and clinical studies, they are promising for the future development of multi-mechanistic therapies.

3.1.2. Anti-Excitatory Treatments

The processes underlying TBI-induced excitotoxicity begin within seconds of the initial trauma, with dysfunction of the cell membrane and ion channels leading to increased intracellular calcium ($[Ca^{2+}]_i$) [25]. This increase in $[Ca^{2+}]_i$ triggers release of vesicles containing neurotransmitters including glutamate into the synaptic cleft as early as 30 minutes following TBI [25]. Excess glutamate stimulates NMDA and AMPA receptors on nearby neurons, triggering depolarization and increased $[Ca^{2+}]_i$ that propagates a wave of excess excitation [26]. While this excitation is initially tolerable to neurons, mitochondrial failure begins to occur within four hours of trauma, leading to energy depletion, neuronal apoptosis and neurodegeneration [25]. These alterations in $[Ca^{2+}]_i$ have been observed to persist up to seven days after TBI, in association with neuronal dysfunction [27]. Abnormal sprouting of collateral synapses, excitatory potentiation and resulting hyperexcitability is observed in hippocampal neurons within days of TBI, increasing the risk for post-traumatic epillepsy [28].

Many medications are currently available to modulate cerebral excitation, several of which have been studied in TBI [29,30]. As part of a pharmacologic treatment protocol, combinations of antiexcitatory medications including valproic acid, ketamine, perampanel, MK801, felbamate and levetiracetam have shown promise in reducing blood-brain barrier (BBB) disruption, expression of pro-inflammatory genes and cytokines, lesion volume, neuronal death and functional deficits in preclinical TBI models [31–35]. Valproic acid inhibits sodium channels involved in excitatory neurotransmission, as well as increasing levels of the inhibitory neurotransmitter GABA in the CNS, making it useful in targeting the hyperacute post-synaptic excitation [36]. Levetiracetam inhibits the release of excitatory neurotransmitter-containing vesicles, which allows it to target the pre-synaptic neurons and intervene earlier to prevent excess excitation [36]. Ketamine, perampanel, MK801 and felbamate act at least in part through inhibition of NMDA and AMPA receptors, preventing the amplication of excitatory neurotransmission in the hyperacute and acute periods [36].

3.1.3. Anti-Inflammatory Treatments

After TBI, lysis of cells as a result of the primary trauma or early secondary injury releases damage-associated molecular patterns (DAMPs), which are detected by toll-like receptors (TLRs) on nearby microglia [37]. The binding of DAMPs to TLRs activates the NF-kB/MAPK signalling pathway, driving secretion of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interkeukin 1-beta (IL-1β) and interleukin 6 (IL-6), with levels of these cytokines peaking within 1-2 days of the initial injury [37,38]. These cytokines activate nearby astrocytes and microglia, amplifying the pro-inflammatory signal and recruting cerebral microglia and astrocytes as well as peripheral immune cells to the site of injury [38]. This neuroinflammatory response to TBI leads to neuronal and glial dysfunction, worsening secondary injury and preventing repair of damaged cells [39]. Recruitment of local microglia is rapid, taking place within hours, while peripheral immune cells reach peak levels within the CNS 1-3 days following injury [38]. Microglia continue to be activated and recuited to the lesion for weeks to months following TBI [37,38,40]. Of note, microglia initially demonstrate an anti-inflammatory M2 phenotype peaking at one week post-injury, but at the 3-4 week point a transition to the pro-inflammatory M1 phenotype is observed [37,38].

There have been several preclinical studies investigating combinations of anti-inflammatory medications to minimize neuroinflammation-associated secondary injury after TBI. Combinations of anti-inflammatory therapies including doxycycline, minocycline, dexamethasone and etanercept have been trialed as part of a pharmacologic treatment approach and demonstrated reductions in pro-inflammatory cytokines, lesion volumes, BBB disruption and neurobehavioral deficits in addition to beneficial effects on glial cells and reductions in neuroinflammation [41–48]. Minocycline and doxycycline inhibit the mechanisms used by peripheral immune cells to enter the CNS, making them likely best applied in the late acute phase of TBI when neutrophils and macrophages are entering the lesion [49]. Etanercept decreases free TNF-α levels, which may reduce the burden of pro-inflammatory cytokines and decrease immune cell activation in the acute phase of TBI [39]. Dexamethasone and other corticosteroids act through inhibition of NF-kB/MAPK signalling therefore preventing downstream secretion of cytokines, making them useful if applied immediately after the generation of DAMPs [39].

3.1.4. Combined Multitarget Pharmacologic Therapies

While it is useful to discuss these mechanisms of secondary injury as separate and distinct processes, oxidative stress, excitotoxicity and neuroinflammation are concurrent processes that overlap and interact after the brain injury. The infiltration and activation of immune cells in the acute period following TBI leads to the generation of ROS and RNS, futher worsening oxidative stress [8]. Excitotoxicity and oxidative stress are also linked, as excessive excitatory stimulation and mitochondrial stress in the acute phase of TBI leads to the generation of ROS [50]. Furthermore, the NMDA and AMPA receptors involved in propagation of excitotoxicity are linked through the protein PSD95, which not only acts to amplify excitation early in the acute phase of TBI but also activates neuronal nitric oxide synthase, increasing the generation of RNS, with this relationship most apparent 24-48 hours after TBI [26].

Several combinations of pharmacologic interventions have been tested, mostly in the laboratory, to target secondary damage following TBI. Combinations of antioxidant medications including NAC and anti-inflammatory medications have been shown to have beneficial effects on glial cells with reduced neuroinflammation and improved functional outcomes in preclinical studies [41,43–45]. Free radical scavenging antioxidant agents such as lipoic acid and DHA in combination with anti-inflammatory medications including curcumin have been used as an adjunct to neural stem cell grafting, with positive effects on cell graft survivial and neuronal differentiation [51–53]. Combinations of NMDA receptor antagonist anti-excitatory medications such as memantine and endogenous hormones including estrogen have been shown to reduce neuronal death in preclinical models [54,55]. In clinical trials the combination of the anti-excitatory GABA agonist propofol and the opioid fentanyl led to significant reductions in ICP, however long-term outcomes were not reported [56].

3.2. Multimodal Nonpharmacologic Interventions

While the majority of the clinical and preclinical literature has examined pharmacologic interventions for TBI, nonpharmacologic interventions including neuromodulation, lifestyle modification, physical exercise and nutraceuticals have been trialed in clinical and preclinical studies of TBI [57–59]. A treatment approach using combined nonpharmacologic interventions has a similar potential as pharmacologic interventions to address the evolving pathophysiology of TBI-induced secondary injury, modulating different molecular targets at different time points.

After full-text review, 5 studies investigating combinations of nonpharmacologic interventions were included for analysis including 2 clinical trials and 3 preclinical studies (Table 2). While a wide range of nonpharmacologic treatments have been tested in the preclinical and clinical literature, the modalities most often investigated in combination with other treatments were transcranial magnetic stimulation (TMS) and environmental enrichment (EE).

Table 2. Multimodal non-pharmacologic methods used in the treatment of TBI.

Model	Population	Sample Size	%Fem	Intervention	Outcome of Combination Therapy	Reference
				Clinical Trials		
Randomized Prospective	Mild-Moderate Human TBI	166	44%	Cognitive training + rTMS vs. Cognitive training alone	Improved neurologic and functional outcomes in chronic TBI rehabilitation	Zhou, 2021

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2023 doi:10.20944/preprints202302.0471.v1

Case Report	Severe Human TBI	1	0%	rTMS + Neuromotor training	Improved motor function in chronic TBI rehabilitation	Martino Cinnera, 2016
				Preclinical Trials		
CCI	Rat	97	0%	TMS + EE vs. TMS alone	Improved motor and sensory function	Shin, 2018
FPI	Rat	46	0%	EE + MEOS vs. EE alone	Improved neurocognitive dysfunction	Maegele, 2005
FPI	Rat	24	0%	EE + MEOS vs. EE alone	Improved neurocognitive dysfunction, reduced neuronal apoptosis and astrocyte activation	Maegele, 2005

3.2.1. Clinical Trials

TMS is a noninvasive form of neuromodulation that has been widely applied in TBI due to promising initial results in neuroprotection and recovery in preclinical models [60,61]. While the molecular mechanisms underlying the effects of TMS are not fully understood, in models of cerebral ischemia TMS has shown the ability to modulate neuroinflammation through inhibition of NF-kB and promotion of microglia M2 polarization [62], as well as antioxidant effects through upregulation of antioxidant enzyme transcription factors [63], making TMS theoretically a useful intervention early in the acute phase of TBI. TMS has been extensively applied as a monomodal therapy, but has also been used in two clinical trials as part of a combination. The first clinical trial investigates the use of TMS and intensive neuromotor training in a patient with chronic neurologic deficits following severe TBI [64]. In this report, the multimodal therapy resulted in improved motor recovery, balance and walking ability. A larger prospective trial investigated combined therapy with TMS and neurocognitive rehabilitation in patients after mild to moderate TBI, with improvement in neurologic and functional outcomes versus rehabilitation alone [65]. The same paper also found improvement in cerebral metabolomics as measured by MRS in the group receiving combined therapy. However, it is important to note that both clinical trials implemented TMS as part of a long-term rehabilitation protocol weeks to months following the primary injury. At this "chronic" stage of TBI and the pathophysiological processes may have little resemblance to the acute phase. To date, no clinical trials have reported outcomes of combined nonpharmacologic interventions in the acute phase of TBI.

3.2.2. Preclinical Trials

EE is an environment that provides enhanced cognitive, physical and social stimulation, which is thought to help prevent deterioration following TBI [66]. While well-studied as a single intervention, several preclinical studies have examined EE as part of a combined treatment approach in which it reduced neuronal apoptosis and astrocyte activation with resulting improvements in neurocognitive dysfunction [67,68]. As part of a multimodal treatment paradigm including EE, TMS was also found to improve motor and sensory function after TBI [69].

3.3. Multimodal Combined Pharmacologic and Nonpharmacologic Interventions

Following full-text review 13 articles were identified as investigating a combination of pharmacologic and nonpharmacologic interventions following TBI, all but 1 of which were studied in the context of preclinical trials (Table 3).

EE has been used as part of a multimodal treatment protocol with the anxiolytic buspirone or the dopamine agonists amantidine or galantamine [70–73]. In the majority of cases, EE and the pharmacologic intervention were each beneficial but had no additional benefit when combined. In one study, however, multimodal treatment with EE and buspirone improved functional outcomes in comparison to the individual treatments [72]. Several other pharmacologic and nonpharmacologic modalities have been explored in combination for the prevention of secondary injury following TBI. Theraputic hypothermia and the growth factor FGF2 were each individually beneficial in improving lesion volume and resulting neurobehavioral outcomes, but had no additional benefit when combined [74]. Other studies involving theraputic hypothermia have been mixed, with a benefit versus monomodal therapies when combined with stem cells in preclinical studies [75] but worse outcomes when combined with progesterone in a large clinical trial [76]. Voluntary physical exercise, in combination with the endogenous compound citicoline demonstrated reductions in lesion volumes and neurobehavioral outcomes after TBI, but there was no benefit to combined therapy compared to the individual interventions [77]. Lastly, a more recent study investigated the combination of mesenchymal stem cell (MSC) grafting with low-intensity transcranial ultrasound (LITUS) [78]. The authors found that MSC grafting improved lesion volume and neurobehavioral outcomes, and this could be significantly improved with the application of LITUS. Furthermore, the authors found that this effect was mediated in part via induction of brain-derived neurotrophic factor (BDNF) and reductions in TNF-α and aquaporin-4 expression.

Table 3. Combinations of pharmacologic and non-pharmacologic interventions studied in preclinical models of TBI.

Model	Species	Sample Size	%Fem	Intervention	Outcome	Reference
				Clinical Trials		
Randomized Placebo Controlled Trial	Human Severe TBI	107	15.9%	"Progesterone + Hypothermia" vs. progesterone or hypothermia alone	Worse long-term outcomes in combined group vs. individual therapies in acute TBI	Sinha, 2017
				Preclinical Trials		
rmCCI	Rat	40	0%	"Amantadine + tDCS" vs. amantadine or tDCS alone	Improved neurobehavioral outcomes, decreased astrocyte activation	Han, 2022
CCI	Rat	90	0%	"MSC + LITUS" vs. MSC or LITUS alone	Improved lesion volume and neurobehavioral outcomes, mediated through induction of BDNF and reduction of TNF-α and AQP4	Yao, 2022
CCI	Rat	68	0%	"Citalopram + EE" vs. citalopram or EE alone	Improved learning and cognitive flexibility	Minchew, 2021
FPI	Rat	96	0%	"BMSC + Hypothermia" vs. BMSC or hypothermia alone	Decreased neuronal apoptosis and neurobehavioral defects	Song, 2020
CCI	Rat	60	0%	"Amantadine + EE" vs. amantadine or EE alone	Improved lesion volume and neurobehavioral outcomes, no additional benefit versus monotherapy	Bleimeister, 2019
CCI	Rat	72	0%	"Galantamine + EE" vs. galantamine or EE alone	Improved lesion volume and neurobehavioral outcomes, no additional benefit versus monotherapy	de la Tremblaye, 2017
CCI	Rat	48	0%	"Methylphenidate + EE" vs. methylphenidate or EE alone	Improved neurobehavioral outcomes, no	Leary, 2017

					additional benefit versus monotherapy	
CCI	Rat	48	0%	"Citicoline + exercise" vs. citicoline or physical exercise alone	Improved lesion volume and neurobehavioral outcomes, no additional benefit versus monotherapy	Jacotte-Simancas, 2015
CCI	Rat	78	0%	"Buspirone + EE" vs. EE or buspirone alone	Improved functional outcomes	Monaco, 2014
CCI	Rat	60	0%	"Buspirone + EE" vs. EE or buspirone alone	Improved functional outcomes, no additional benefit versus monotherapy	Kline, 2012
CCI	Rat	65	0%	"8-OH-DPAT + EE" vs. EE or 8-OH-DPAT alone	Decreased neuronal loss, no additional benefit versus monotherapy	Kline, 2010
CCI	Rat	50	0%	"FGF-2 + Hypothermia" vs. Hypothermia or FGF-2 alone	Improved lesion volume and neurobehavioral outcomes, no additional benefit versus monotherapy	Yan, 2000

3.4. Multimodal Neuromonitoring

Multimodal neuromonitoring (MMM) entails the measurement and integration of multiple biological parameters to better understand a patient's pathophysiologic state and guide treatment decisions [79]. Measurement of cerebral physical, metabolic and electrical physiologic parameters through MMM sensors allows for the collection of a wide range of physiologic and pathophysiological data. When interpreted and analyzed, insights gained from MMM can help determine what interventions, if any, are needed to optimize cerebral physiology [11]. The rationale for MMM is thus to convert the heterogenous pathophysiology of TBI into an array of disctinct physiologic variables that may be more or less amenable to different forms of treatment at different time periods.

After full-text review, 12 articles were included for analysis (Table 4). Of note, while MMM has been extensively studied, articles were only included if they examined outcomes resulting from a combination of two or more different biological parameters in the context of MMM-guided treatment of TBI. Studies examining measurement parameters and implementation strategies alone, as well as studies not reporting outcomes or use of MMM to guide treatment were excluded. The most common physical parameters measured alongside ICP were brain tissue oxygenation ($P_{bt}O_2$), cerebral perfusion pressure (CCP), and sometimes cerebrovascular pressure reactivity (PRx). Metabolic brain parameters including brain tissue pH and lactate-pyruvate ratio (LPR) can be measured using cerebral microdialysis (CMD) and jugular venous oxygen saturation ($S_{jv}O_2$) measurement can be used used to estimate cerebral oxygen extraction capability.

Table 4. Multimodal neuromonitoring studied in the setting of TBI.

TBI Severity	Study Design	Sample Size	%Fem	Neuromonitoring Parameters	Outcome of MMM-Guided Treatment	Reference
			Clinical Trials			
Moderate-Severe	Retrospective Observational	61	29.5%	ICP, CPP, PRx	May predict need for long term treatment of seizures after TBI	Appavu, 2022
Severe	Retrospective Cohort	49	20.4%	ICP, $P_{bt}O_2$, CPP	Improved treatment of cerebral hypoxia and	Lang, 2022

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2023 doi:10.20944/preprints202302.0471.v1

					hypertension without improvement in long term outcomes	
Severe	Retrospective Observational	20	15%	ICP, CPP, $P_{bt}O_2$, LPR	Enabled diagnosis and treatment of cerebral metabolic crisis	Marini, 2022
Moderate-Severe	Prospective Interventional	5	100%	ICP, $P_{bt}O_2$, LPR	Improved cerebral metabolic dysfunction	Khellaf, 2022
Severe	Case Report	1	0%	ICP, $P_{bt}O_2$, CPP, PRx,	Guided need for surgical intervention	Robinson, 2021
Moderate-Severe	Retrospective Observational	85	31.8%	ICP, CPP, PRx	Helped guide clinical treatment in pediatric TBI, reduced length of time on mechanical ventilation	Appavu, 2021
Severe	Retrospective Observational	81	19.8%	ICP, CPP, PRx	Improved clinical outcomes	Petkus, 2020
Moderate-Severe	Retrospective Observational	38	32%	ICP, CPP, $P_{bt}O_2$, PaO_2	Characterized etiology of cerebral hypoxemia and guided treatment	Dellazizzo, 2018
Severe	Prospective Randomized Cohort	119	21%	ICP, $P_{bt}O_2$	Reduced hypoxia with trend toward better outcomes than ICP alone	Okonkwo, 2017
Moderate-Severe	Retrospective Cohort	30	10%	ICP, CPP	Reduced mortality and length of ICU stay	Luca, 2015
Severe	Prospective Observational	18	38.9%	ICP, CPP	Reduced mortality and improved long-term neurologic outcomes	Dunham, 2006
Severe	Prospective Randomized Cohort	82	15.9%	ICP, CPP, $P_{bt}O_2$, CBF, pH, $SvjO_2$, PRx	Treatment guided by MMM associated with improved outcomes	Isa, 2003

3.4.1. Multimodal Neuromitoring-Guided Treatment

Among the most commonly studied MMM parameters are intracranial pressure (ICP), cerebral perfusion pressure (CPP) and cerebrovascular autoregulatory capability (PRx). As elevated ICP reduces CPP and prevents optimal brain perfusion, evidence-based guidelines recommend ICP monitoring for patients with severe TBI [9,79,80], as well as estabishing ICP and CPP-based thresholds for pharmacologic and surgical interventions [9]. TBI treatment based on MMM-derived optimal cerebral perfusion has demonstrated improved clinical outcomes, especially in older patients who may have reduced autoregulatory capacity [81]. PRx allows for real-time measurement of cerebrovascular autoregulation [82] and may help to predict the need for surgical intervention in severe TBI [83–85]. Measurement of brain oxygenation parameters such as $P_{bt}O_2$ allows for rapid implementation of theraputic interventions to correct cerebral hypoxia [82,86], and measurement of $P_{bt}O_2$ and ICP in the BOOST-II trial was suggested to improve secondary injury after TBI demonstrating the potential effect of such early interventions [87]. Measurement of $P_{bt}O_2$, CPP and arterial oxygen saturation has been used to guide treatment of cerebral hypoxia in severe TBI, helping to uncover physiologic states that may lead to impaired brain oxygen metabolism [88]. CMD-based parameters including LPR and pH can directly characterize cerebral metabolic states including ischemia, metabolic stress and mitochondrial dysfunction [79,89], and has been shown to predict cerebral metabolic crisis and disruptions in cerebral perfusion requiring theraputic intervention [90,91]. The identification of metabolic derangement including mitochodrial dysfunction via CMD-based MMM has also been used to guide targeted metabolic treatment of TBI [92].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2023 doi:10.20944/preprints202302.0471.v1

4. Discussion

Traumatic brain injury (TBI) is one of the most common global causes of morbidity and mortality [1,2]. Despite many decades of concerted effort, a highly effective treatment for this condition remains elusive [93]. Considering the multifactorial pathophysiology of TBI, a treatment paradigm combining interventions targeting more than one aspect of TBI pathophysiology has been suggested as the goal for ongoing and future research [5]. However, to date these combination therapies have demonstrated mixed results [6].

The available literature suggests that the reason for this lack of success may be that these combination therapies have not addressed the evolution of TBI pathophysiology over time. In recent years, the scientific understanding of pathophysiology driving secondary injury after TBI has grown immensely [2,3,12,26]. It is now well established that the mechanisms underlying key drivers of secondary injury, such as inflammation and oxidative stress, are not static but undergo change over time [8,25,94]. With this understanding it may be possible to predict what cellular and molecular mechanisms are most likely contributing to secondary injury at a particular stage of injury, however it is known that patients show a high degree of variability in their pathophysiologic response following TBI [95]. Therefore, combined treatments must be based on not only a detailed understanding of "typical" secondary injury evolution but also refined and fine-tuned in accordance with the patient's individual development of secondary injury to best treat TBI. It is possible that a multimodal treatment paradigm may address the evolving pathophysiology of secondary injury through judicious application of pharmacologic and/or nonpharmacologic interventions that are informed by multimodal imaging and neuromonitoring. By addressing not only the multifactorial causes of secondary injury, but also how they change as the disease progresses, multimodal treatment may have the potential to succeed where combination therapies failed.

4.1. Current State of Multimodal TBI Treatment

While it is increasingly appreciated that clinical TBI is a heterogeneous group of disease processes rather than a single disease, the temporal evolution of TBI-induced secondary injury has been less well investigated in the setting of TBI treatment [7], which may contribute to the current gap in outcomes between preclinical and clinical studies. The primary drivers of TBI-associated secondary injury can be broadly divided into the categories of neuroinflammation, oxidative stress and excitotoxicity, although many other mechanisms including mitochondrial failure and cerebral edema may also play a role. Each of these is not a static disease state, but rather an evolving disease process. For example, in the hyperacute state, neuroinflammation in TBI is driven by DAMP-induced activation of local brain tissue microglia, leading to secretion of pro-inflammatory cytokines within hours of the injury occurring [37]. However, in the acute period within days of the injury infiltration of peripheral immune cells contributes more to neuroinflammation, and at the 3-4 week time point pro-inflammatory M1 microglial activation becomes a prominent driver of the inflammatory process [38]. Given this it is possible that, for example, an intervention targeting polarization of microglia from the M1 to the anti-inflammatory M2 phenotype may be largely ineffective if given in the acute phase but may show benefit in the early chronic phase of secondary injury.

Additionally, treatment for secondary injury after TBI is most commonly directed at stopping or preventing secondary insults such as hypotension or cerebral edema that can occur in the absence of careful management [9,12,96]. Treatment approaches focusing on the underlying physiological changes of secondary injury such as excitotoxicity and neuroinflammation are less commonly reported [97,98]. It is thus important to not conflate secondary insults with the pathophysiology of secondary injury in comparing treatment paradigms.

Many pharmacologic interventions have been trialed to prevent or reduce secondary injury resulting from TBI. In preclinical models, an extensive number of medications have been tested to prevent secondary injury, and nearly all tested combinations have demonstrated some degree of improvement in neurobehavioral outcomes and lesion volume after experimental TBI (Table 3). However, none have been clinically successful to date as a monotherapy or combination therapy [5,6]. A multimodal treatment approach taking into account the evolving pathophysiology of TBI may be the key for clinically successful treatments of secondary injury. While there are some promising preclinical trials testing a similar method [19], there have been no clinical trials to date investigating this multimodal treatment strategy. While there are many potential options for targeted multimodal treatments, one option for pre-screening medications likely to be effective is to trial medications that showed promise in preclinical and early clinical (phase I-II) trials but did not show a benefit in phase III clinical trials. These medications have an established safety profile and proven mechanism, and it is possible that some of them may have had potential to be effective but were not applied in a multimodal manner, at the optimal time point based on the evolution of TBI pathophysiology and the patients' physiologic state.

While the pathophysiologic mechanisms driving secondary injury have been better characterized in recent years, much of the research uncovering these mechanisms has been performed in male animal models or male patients [99]. For example, in the preclinical trials examined within this paper only three out of fifty-four studies (6%) included female animals, and the average percentage of female subjects within analyzed clinical studies was 24%. The pathophysiologic mechanisms underlying primary and secondary injury following TBI are likely more similar than different males and females, however some differences are known to exist between males and females in TBI. In preclinical models of TBI, female animals have demonstrated decreased neuroinflammation including reductions in reactive microglia and infiltrating peripheral immune cells [100,101], decreased BBB disruption [102], and decreased oxidative stress [103]. While the mechanistic differences in TBI pathophysiology are complex and still under investigation, the effect of female sex steroids including estrogen and progesterone has been suggested as a key underlying driver for these observed differences [104]. In animal models, female sex hormones including estrogen and progesterone have shown efficacy as part of monomodal and combined therapies [55,105,106]. However, clinical trials of estrogen and progesterone as therapies for TBI have not been widely successful, which has been suggested to result from failure to account for physiologic differences in sex hormones due to age and biologic sex at the point of treatment [104]. The discrepancy between preclinical studies, in which female animals typically experience better outcomes, and clinical trials in which females typically experience worse outcomes [99] additionally highlights the need for better understanding of sex differences in TBI pathophysiology and the need to consider sex hormonal levels as an important physiologic parameter that could help guide multimodal treatment.

4.2. Future Directions in Multimodal TBI Treatment

While the prevention of secondary injury following TBI remains a challenge for clinicians, there are several promising avenues for multimodal TBI interventions that are undergoing active research.

As the temporal evolution of TBI-induced secondary injury has become increasingly well understood, so too has grown understanding of the spatial differences in TBI pathophysiology and how this may guide treatment decisions. In TBI there exist regions of contused brain tissue injured by direct trauma, surrounded by areas of peri-contusional tissue that experience ischemia and metabolic disruption resulting from secondary injury [107,108]. These regions experience differing degrees of secondary injury, with oxidative stress and mitochondrial dysfunction shown to be more severe in contused brain tissue than the peri-contusional region [109]. While the contused areas experience severe metabolic and mitochondrial dysfunction that can culminate in unregulated cellular necrosis, the peri-contusional tissue typically maintains sufficient mitochondrial and metabolic function to initiate transcription of protective genes regulating cellular repair processes [97]. This is a critical distinction, as therapeutics that rely on specific cellular pathways may be viable in the peri-contusional tissue but less so in the contused tissue which lacks the resources to maintain normal cellular processes. For example, glucocorticoids have the potential to reduce edema and inflammation following TBI, but act through activation of transcription factors that induce various downstream effector proteins [110]. In a large randomized clinical trial, administration of glucocorticoids was associated with an increased risk of death compared to placebo, which may result from this mechanistic failure and increased demand on already stressed cells [111]. A better understanding of the relative distribution of contused and peri-contused tissue in an individual

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2023 doi:10.20944/preprints202302.0471.v1

patient may offer insights into the efficacy of a particular treatment or combination of interventions, however this approach has not yet been tested in clinical studies.

Non-pharmacologic interventions offer some promise in the multimodal treatment of secondary injury after TBI, for several reasons. Many non-pharmacologic interventions such as neuromodulation and nutraceuticals can be initiated without disrupting ongoing treatment and have a favorable risk/benefit profile [57,58], which makes it easier to apply them alongside other therapies to address TBI as it evolves. However, much like for pharmacologic interventions, the blind application of non-pharmacologic treatment techniques without a detailed understanding of the patient's physiologic state at the time of application as well as knowledge of the molecular targets of the intervention is likely to fail. As an example, TMS has been shown in ischemic brain tissue to work in part through induction of anti-oxidative enzymes [63] and inhibition of NF-kB [62], suggesting that TMS may be most effective if applied as part of a multimodal treatment regimen in the acute phase of TBI. Just as multimodal imaging and neuromonitoring have shown potential to guide pharmacologic therapies for TBI, they have also helped inform non-pharmacologic treatments. Several groups have used MMM parameters including ICP, CPP, TCD and $P_{bt}O_2$ to guide the use of therapeutic hypothermia in patients with severe TBI [112,113]. Additionally, applying a combination of pharmacologic and non-pharmacologic interventions is a possible means to address the pathophysiology of TBI and TBI-associated secondary damage, as non-pharmacologic interventions can target similar mechanisms of secondary injury through different targets in a multimodal approach to TBI treatment. For example, a hypothetical combination of mild therapeutic hypothermia and a free radical scavenger would target oxidative stress through decreasing ROS/RNS and upregulating anti-oxidative enzymes, potentially impacting oxidative stress at the hyperacute and early acute time periods [14,114]. While non-pharmacologic interventions are an appealing avenue for treatment of TBI, the mechanisms that underlie these interventions are not always well characterized. When the cellular and molecular targets of non-pharmacologic interventions for TBI are better understood, they may be a powerful tool for multimodal treatment of TBI.

Harnessing endogenous mechanisms with an inherent capability to activate multiple cellular pathways may allow for the targeting of TBI-induced secondary injury at distinct time points, which serves as the foundation for investigation of endogenous mechanisms as part of a multimodal treatment paradigm. Implemented in this fashion, it is possible that endogenous mechanisms may mimic the effects seen with administration of multiple pharmacologic treatments, potentially without the associated logistical challenges. Conditioning is a widely applied therapeutic technique in which a potentially harmful stimuli is applied below the threshold for tissue damage, leading to the induction of endogenous neuroprotective pathways [115]. Remote ischemic post-conditioning is a conditioning mechanism widely studied in ischemic stroke and found to be safe and effective in both preclinical and clinical studies [116,117], and has demonstrated promising results in TBI [118,119]. While the mechanistic effects underlying ischemic post-conditioning are still being uncovered, it is known to increase expression of BDNF and promote neurogenesis and neuroplasticity, which may help to prevent neurodegeneration and maladaptive functional alterations following cerebral insults [115]. Ischemic post-conditioning may thus be most effective if applied in the subacute and early chronic phases, to promote neuronal repair and functional recovery following TBI. The beneficial effects of conditioning-activated endogenous pathways parallel the investigation of therapeutic hypothermia for TBI, developed out of the observation that hibernating animals display resistance against TBI [120,121]. While preclinical trials have shown promise for therapeutic hypothermia, the available clinical literature does not demonstrate a mortality benefit from therapeutic hypothermia in adults [122,123]. However, this may act to reiterate the point that, with a disease as complex as TBI, it is necessary to apply a treatment at exactly the right point in disease progression, thus necessitating the implementation of therapeutic hypothermia as part of a multimodal treatment plan including multimodal imaging and monitoring based assessment of individual physiology. In fact, recent work has investigated the optimal timing of therapeutic hypothermia in preclinical studies [124], and a clinical trial has used CMD to guide therapeutic hypothermia with a resulting reduction in mortality [125] demonstrating the feasibility of such an approach. Though not yet assessed in TBI, the diving

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2023 doi:10.20944/preprints202302.0471.v1

reflex is yet another endogenous mechanism that may be harnessed. Triggered when trigeminal sensory afferents are activated, such as by cold water during diving, a constellation of mechanisms, most notably driving blood away from the periphery and towards the brain, are produced [126]. Far from only increasing the flow of blood to the brain, activation of the diving reflex initiates the development of an anti-oxidative phenotype, both reducing the level of systemic ROS [127] and increasing antioxidant enzyme activity levels [128,129]. A systemic anti-inflammatory state is seen with chronic activation of the diving reflex [130,131], which may be due to the effects of the diving reflex being mediated in part through the vagus nerve, well known for its modulation of the inflammatory complex [132,133]. If applied judiciously, as part of a multimodal treatment strategy, the diving reflex thus could be used to target both the acute and subacute stages in oxidative stress development. Given these factors, it is possible that the diving reflex may be able to target multiple points in the timeline of TBI's pathogenic progression and represents a promising avenue for future research. The ability of endogenous mechanisms to modulate cellular pathways is attractive in the treatment of TBI.

4.3. Imaging- & Neuromonitoring-Guided Treatment

Multimodal imaging represents a wide array of imaging techniques that are able to integrate structural and functional information in TBI, correlating regions of abnormal anatomy with disruptions in CNS function [134]. This is particularly important for mild TBI (mTBI) in which objective diagnosis and initiation of treatment is sometimes only possible with multimodal imaging techniques [135–137]. In moderate and severe TBI multimodal imaging historically plays a greater role in prognostication and determining the need and appropriateness of aggressive interventions [138,139]. Multimodal MRI has been studied in clinical trials, predominantly in mTBI in the subacute or chronic phase, as it is available in most academic medical centers and does not expose the patient to ionizing radiation [137,140] MRI sequences including diffusion weighted imaging (DWI) can be used to image cerebral edema following TBI, even in the first few days following injury [141,142], which could guide the early administration of therapies to reduce edema [12]. Other advanced MRI sequences such as functional MRI (fMRI) and magnetic resonance specroscopy (MRS) may have a role in guiding treatment decisions after TBI. fMRI measures changes in blood oxygen levels associated with neuronal activation to track brain activity in real time [143], and can localize foci of post-TBI epilepsy even in the absence of visible structural lesions [144] which may allow for early initiation of antiepileptic medications in high risk patients in conjunction with other clinical data [145]. MRS is a non-invasive means of characterizing cerebral metabolites at the molecular level [146], and has been used to assess neuroinflammation in preclinical models of TBI [147,148]. It has been proposed that a noninvasive means to detect neuroinflammation including MRS and novel PET radiotracers specific to activated glial cells could be used to guide optimal timing of anti-inflammatory therapies in TBI [149]. In this way, multimodal imaging techniques may be able to evaluate aspects of TBI-induced secondary injury at the micro-scale and fine-tune treatment. For example, a novel PET radiotracer specific to M2-activated microglia has been developed and tested in preclinical models [150], which has the potential to refine treatments promoting anti-inflammatory effects of M2 microglia. However, multimodal MRI techniques have not yet been shown to have utility in timing treatments of TBI. Furthermore, multimodal MRI has been best studied in mTBI outside of the acute phase of injury [137], while the physiologic insights possible with multimodal MRI would likely be most useful in the acute phase of moderate and severe TBI. Multimodal imaging including MRI is difficult to perform in this population due to the practical difficulties of transporting a critically ill patient out of the intensive care unit for long imaging procedures, or placing an intubated and mechanically ventillated patient into the MRI scanner [151]. This critical patient population is thus generally unable to benefit from multimodal MRI, and prognostication is typically done using non-multimodal imaging such as CT scans [152,153].

Several groups have trialed methods to reduce the limitations associated with multimodal imaging as an adjunct to the treatment of TBI. Portable imaging devices have been developed that can be brought to the patient's bedside, removing the logistical challenges and risk associated with

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2023 doi:10.20944/preprints202302.0471.v1

transferring a critically ill or injured patient [154]. Portable low-field multimodal MRI has shown potential to refine treatment in the neurocritical care setting [155], however the resulting images are significantly lower in quality as compared to a traditional MRI which limits clinical utility. Another method to reduce the limitations of multimodal imaging is the creation of longitudinal prospective multi-institutional studies to standardize imaging techniques and link acute imaging results with long-term functional outcomes. One such example is the TRACK-TBI study, which has leveraged this model to uncover early multimodal imaging markers in mTBI that predict long-term outcomes [156]. Furthermore, the data generated by studies like TRACK-TBI can be used to train, validate and test machine learning models to uncover prognostic insights into TBI physiology that could be used to guide treatment. Various forms of machine learning models have been used to generate prognostic insights into TBI based on multimodal imaging data, including convolutional neural networks [157] and linear support vector machine analysis [158]. It has been suggested that prognostic inormation derived from machine learning models may help guide clinical treatment decisions including appropriateness of aggressive therapies [159].

In its current form, multimodal neuromonitoring (MMM) consists of collecting and deriving a wide range of cerebral physiologic data, including cerebral physical, hemodynamic, metabolic and electrophysiologic parameters, which are collected and output as a continuous stream of high-frequency data points [82]. This real time tracking of cerebral physiology has great potential to guide multimodal treatment of secondary injury following TBI. Certain parameters (ICP, $P_{bt}O_2$) have reliably shown to be effective in guiding treatment of moderate and severely injured TBI patients [160,161]. Ischemia and metabolic disruption in TBI leads to abnormal and pathologic electrical events including cortical spreading depolarizations (CSDs) whch are common after TBI and known to play a role in secondary injury [29,162–164]. Reliable means of identifying and targeting CSDs in TBI has been proposed to be a major need in the current landscape of TBI treatment [162,165,166], thus placing electrophysiologic MMM techniques in a valuable role for the guidance of theraputic interventions targeting mechanisms underlying secondary injury in TBI. While no work to date has identified a multimodal treatment for CSDs in TBI, a recent paper showed a benefit from ketamine in multiple preclinical models of CSD [167], which in conjunction with the successes of ketamine as a multimodal treatment [33], suggests it may have potential for the multimodal treatment of CSDs.

Currently, many advanced technologies exist for MMM, allowing for real-time acquisition of extensive physiologic and pathophysiological data from patients with TBI. However, MMM has a major operational limitation in that modern MMM generates such high volumes of data that drawing treatment-guiding conclusions is challenging for clinicians [151]. Additionally, there is a lack of clinical guidelines for the interpretation of the majority of this data, with the most recent Brain Trauma Foundation guidelines including recommendations only on multimodal measurement of ICP, CPP and $S_{jv}O_2$-based arteriovenous oxygen content difference due to their known potential for guiding treatment decisions [9]. Thus modern MMM produces a high volume of data on multiple physiologic parameters, without a large degree of guidance for clinicians caring for patients with TBI. Several recent groups have advocated for the use of machine learning and "big data" analytic approaches to synthesize this information and classify patients into distinct physiologic states, allowing for an individualized yet systematic approach to treating the evolving physiologic derangements caused by TBI [11,168,169]. For example, while the BOOST-II trial was not statistically powered to guide outcomes-oriented treatment, a machine learning analysis of BOOST-II data used a combination of logistic regression, elastic net and random forest machine learning methods to derive clinically applicable predictive models for ICP and brain oxygenation that could be used for early intervention and treatment of intracanial hypertension and hypoxia [170]. Moving forward, future work linking large high-fidelity data sets of MMM-derived physiologic data with long term clinical outcomes could be used to further drive advances in TBI treatment [151,171]. For example, the Targeted Evaulation, Action and Monitoring group integrates a large volume of clinical monitoring data to categorize patients by disease phenotype and deploy a targeted treatment plan based on their clinical status, with the ability to reassess and determine the need for future treatments [11]. Another novel approach is to integrate TBI serum biomarkers with information from multimodal imaging and MMM to create a individualized "-omics" data set (proteomics, metabolomics, physiomics, etc.), which through extensive machine learning analysis can lead to development of a comprehensive physiology-based theraputic plan [151].

MMM-guided treatment for TBI is a promising componant of a multimodal treatment paradigm, but has several limitations that may affect implementation. It has been argued that the parameters measured in MMM may only reflect micro-scale physiology in a particular brain region, not the CNS as a whole [172]. A combination of intraparenchymal sensors has shown promise in better characterizing the general cerebral enviroment and local hemodynamics, however these results must be validated with more established techniques [173]. While the data derived from MMM can effectively guide treatment [82,174], the invasiveness of MMM probes has limited MMM to use in moderate and severe TBI. Invasive MMM is generally considered safe [175], however noninvasive approaches to MMM could expand its use to the mTBI population. Noninvasive measurements of ICP including optic nerve sheath diameter have been shown to correlate with invasive ICP measurement techniques and help guide surgical management of TBI [83,176], and thus may allow MMM to guide treatment in mTBI without insertion of invasive monitoring devices. However noninvasive techniques have significant variation in inter-user reliability [177], and have not desmonstrated an ability to monitor changes in ICP over time [178], which significantly limits their ability to guide treatment.

4.5. Limitations

This review is not without limitations. While our primary literature review was extensive, encompassing more than 4,000 primary sources, the heterogeneity of the TBI literature and the wide variety of research methods used make it possible that some articles may have been missed by our search. The studies found included a wide variety of injury severity (mild to severe) and time after injury (acute, subacute to chronic). Additionally, many multimodal monitoring and imaging techniques can give insight into the ongoing secondary insults following TBI (cerebral edema, elevated ICP, etc.), but do not necessarily measure changes in underlying pathophysiology which at times must be inferred. Lastly, while multimodal imaging, neuromonitoring, and therapeutic interventions are well studied in TBI, an operational definition is not always available for all studies. What exactly is or is not "multimodal" thus has a degree of variability that makes comparisons between studies more challenging. Our definitions of multimodal diagnostic and therapeutic techniques are based upon a synthesis of the available literature, but other groups may find other operational definitions more useful.

5. Conclusions

TBI is one of the most common global causes of death and disability, with a relative lack of effective treatments. As a disease with heterogeneous pathophysiology including ischemia, oxidative stress, neuroinflammation and excitotoxicity, monomodal treatment paradigms targeting a single aspect of TBI pathophysiology have shown poor results in clinical trials. Despite initial excitement, combination therapies targeting multiple individual mechanisms simultaneously have to date also fallen short of expectations, although there have been relatively few such studies. A multimodal treatment paradigm integrating physiologic information derived in part from multimodal imaging and neuromonitoring can be used to form a pathophysiologic assessment, which may then be treated with targeted pharmacologic and/or non-pharmacologic interventions. Multimodal interventions, both pharmacologic and non-pharmacologic, have shown great promise in preclinical studies but have yet to undergo widespread testing in clinical trials. Multimodal imaging and neuromonitoring have demonstrated the ability to help guide multimodal treatment of TBI, due to insights into prognosis and disease pathophysiology. Future interventions including multi-institutional outcome-driven data sets, refinement of machine learning models, and increasing the study of female TBI pathophysiology represent promising areas of ongoing development in order to fully implement the promise of multi-mechanistic therapeutic approaches.

Author Contributions: Conceptualization, CL; methodology, CL; writing—original draft preparation, DGL; writing—review and editing, RKN, CL, DGL; funding acquisition, CL. All authors have read and agreed to the published version of the manuscript.

Funding: This work is supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under award number R21NS114763, and the US Army Medical Research and Materiel Command (USAMRMC) under award # W81XWH-18-1-0773.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg*. Apr 1 2018:1-18. doi:10.3171/2017.10.JNS17352
2. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management. *Med Clin North Am*. Mar 2020;104(2):213-238. doi:10.1016/j.mcna.2019.11.001
3. Pearn ML, Niesman IR, Egawa J, et al. Pathophysiology Associated with Traumatic Brain Injury: Current Treatments and Potential Novel Therapeutics. *Cell Mol Neurobiol*. May 2017;37(4):571-585. doi:10.1007/s10571-016-0400-1
4. Stocchetti N, Carbonara M, Citerio G, et al. Severe traumatic brain injury: targeted management in the intensive care unit. *The Lancet Neurology*. 2017;16(6):452-464. doi:10.1016/s1474-4422(17)30118-7
5. Margulies S, Hicks R, Combination Therapies for Traumatic Brain Injury Workshop L. Combination therapies for traumatic brain injury: prospective considerations. *J Neurotrauma*. Jun 2009;26(6):925-39. doi:10.1089/neu.2008-079410.1089/neu.2008.0794
6. Margulies S, Anderson G, Atif F, et al. Combination Therapies for Traumatic Brain Injury: Retrospective Considerations. *J Neurotrauma*. Jan 1 2016;33(1):101-12. doi:10.1089/neu.2014.3855
7. Somayaji MR, Przekwas AJ, Gupta RK. Combination Therapy for Multi-Target Manipulation of Secondary Brain Injury Mechanisms. *Curr Neuropharmacol*. 2018;16(4):484-504. doi:10.2174/1570159X15666170828165711
8. Fesharaki-Zadeh A. Oxidative Stress in Traumatic Brain Injury. *Int J Mol Sci*. Oct 27 2022;23(21)doi:10.3390/ijms232113000
9. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery*. Jan 1 2017;80(1):6-15. doi:10.1227/NEU.0000000000001432
10. Doppenberg EM, Choi SC, Bullock R. Clinical trials in traumatic brain injury: lessons for the future. *J Neurosurg Anesthesiol*. Jan 2004;16(1):87-94. doi:10.1097/00008506-200401000-00019
11. Kochanek PM, Jackson TC, Jha RM, et al. Paths to Successful Translation of New Therapies for Severe Traumatic Brain Injury in the Golden Age of Traumatic Brain Injury Research: A Pittsburgh Vision. *J Neurotrauma*. Nov 15 2020;37(22):2353-2371. doi:10.1089/neu.2018.6203
12. Jha RM, Kochanek PM, Simard JM. Pathophysiology and treatment of cerebral edema in traumatic brain injury. *Neuropharmacology*. Feb 2019;145(Pt B):230-246. doi:10.1016/j.neuropharm.2018.08.004
13. Lee SH, Lee M, Ko DG, Choi BY, Suh SW. The Role of NADPH Oxidase in Neuronal Death and Neurogenesis after Acute Neurological Disorders. *Antioxidants (Basel)*. May 7 2021;10(5)doi:10.3390/antiox10050739
14. Ismail H, Shakkour Z, Tabet M, et al. Traumatic Brain Injury: Oxidative Stress and Novel Anti-Oxidants Such as Mitoquinone and Edaravone. *Antioxidants (Basel)*. Oct 1 2020;9(10)doi:10.3390/antiox9100943
15. DeKosky ST, Taffe KM, Abrahamson EE, Dixon CE, Kochanek PM, Ikonomovic MD. Time course analysis of hippocampal nerve growth factor and antioxidant enzyme activity following lateral controlled cortical impact brain injury in the rat. *J Neurotrauma*. May 2004;21(5):491-500. doi:10.1089/089771504774129838
16. Clark RSB, Empey PE, Bayir H, et al. Phase I randomized clinical trial of N-acetylcysteine in combination with an adjuvant probenecid for treatment of severe traumatic brain injury in children. *PLoS One*. 2017;12(7):e0180280. doi:10.1371/journal.pone.0180280
17. Mader MM, Czorlich P. The role of L-arginine metabolism in neurocritical care patients. *Neural Regen Res*. Jul 2022;17(7):1446-1453. doi:10.4103/1673-5374.327331
18. Cherian L, Robertson CS. L-arginine and free radical scavengers increase cerebral blood flow and brain tissue nitric oxide concentrations after controlled cortical impact injury in rats. *J Neurotrauma*. Jan 2003;20(1):77-85. doi:10.1089/08977150360517209
19. Davis CK, Bathula S, Hsu M, et al. An antioxidant and anti-ER stress combo therapy decreases inflammation, secondary brain damage and promotes neurological recovery following traumatic brain injury in mice. *J Neurosci*. Jul 25 2022;doi:10.1523/JNEUROSCI.0212-22.2022

20. Hou L, Sun F, Huang R, Sun W, Zhang D, Wang Q. Inhibition of NADPH oxidase by apocynin prevents learning and memory deficits in a mouse Parkinson's disease model. *Redox Biol*. Apr 2019;22:101134. doi:10.1016/j.redox.2019.101134
21. Chandran R, Kim T, Mehta SL, et al. A combination antioxidant therapy to inhibit NOX2 and activate Nrf2 decreases secondary brain damage and improves functional recovery after traumatic brain injury. *J Cereb Blood Flow Metab*. Oct 2018;38(10):1818-1827. doi:10.1177/0271678X17738701
22. Saykally JN, Rachmany L, Hatic H, et al. The nuclear factor erythroid 2-like 2 activator, tert-butylhydroquinone, improves cognitive performance in mice after mild traumatic brain injury. *Neuroscience*. Oct 25 2012;223:305-14. doi:10.1016/j.neuroscience.2012.07.070
23. Sokka AL, Putkonen N, Mudo G, et al. Endoplasmic reticulum stress inhibition protects against excitotoxic neuronal injury in the rat brain. *J Neurosci*. Jan 24 2007;27(4):901-8. doi:10.1523/JNEUROSCI.4289-06.2007
24. Nakajima S, Chi Y, Gao K, Kono K, Yao J. eIF2alpha-Independent Inhibition of TNF-alpha-Triggered NF-kappaB Activation by Salubrinal. *Biol Pharm Bull*. 2015;38(9):1368-74. doi:10.1248/bpb.b15-00312
25. Hoffe B, Holahan MR. Hyperacute Excitotoxic Mechanisms and Synaptic Dysfunction Involved in Traumatic Brain Injury. *Front Mol Neurosci*. 2022;15:831825. doi:10.3389/fnmol.2022.831825
26. Jamjoom AAB, Rhodes J, Andrews PJD, Grant SGN. The synapse in traumatic brain injury. *Brain*. Feb 12 2021;144(1):18-31. doi:10.1093/brain/awaa321
27. Deshpande LS, Sun DA, Sombati S, et al. Alterations in neuronal calcium levels are associated with cognitive deficits after traumatic brain injury. *Neurosci Lett*. Aug 15 2008;441(1):115-9. doi:10.1016/j.neulet.2008.05.113
28. Neuberger EJ, Gupta A, Subramanian D, Korgaonkar AA, Santhakumar V. Converging early responses to brain injury pave the road to epileptogenesis. *J Neurosci Res*. Nov 2019;97(11):1335-1344. doi:10.1002/jnr.24202
29. Sueiras M, Thonon V, Santamarina E, et al. Cortical Spreading Depression Phenomena Are Frequent in Ischemic and Traumatic Penumbra: A Prospective Study in Patients With Traumatic Brain Injury and Large Hemispheric Ischemic Stroke. *J Clin Neurophysiol*. Jan 1 2021;38(1):47-55. doi:10.1097/WNP.0000000000000648
30. Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J Cereb Blood Flow Metab*. Jan 2011;31(1):17-35. doi:10.1038/jcbfm.2010.191
31. Yu F, Wang Z, Tanaka M, et al. Posttrauma cotreatment with lithium and valproate: reduction of lesion volume, attenuation of blood-brain barrier disruption, and improvement in motor coordination in mice with traumatic brain injury. *J Neurosurg*. Sep 2013;119(3):766-73. doi:10.3171/2013.6.JNS13135
32. Liu S, Tian H, Niu Y, et al. Combined cell grafting and VPA administration facilitates neural repair through axonal regeneration and synaptogenesis in traumatic brain injury. *Acta Biochim Biophys Sin (Shanghai)*. Aug 25 2022;doi:10.3724/abbs.2022123
33. Alqahtani F, Assiri MA, Mohany M, et al. Coadministration of Ketamine and Perampanel Improves Behavioral Function and Reduces Inflammation in Acute Traumatic Brain Injury Mouse Model. *Biomed Res Int*. 2020;2020:3193725. doi:10.1155/2020/3193725
34. Jenkins LW, Lu YC, Johnston WE, Lyeth BG, Prough DS. Combined therapy affects outcomes differentially after mild traumatic brain injury and secondary forebrain ischemia in rats. *Brain Research*. 1999;817(1-2):132-144. doi:10.1016/s0006-8993(98)01237-2
35. Bayhan I, Turtay MG, Ciftci O, et al. Comparison of immunological, histological and oxidative effects of felbamate and levetiracetam in traumatic brain injury. *Eur Rev Med Pharmacol Sci*. Jun 2020;24(12):7083-7091. doi:10.26355/eurrev_202006_21702
36. Hanaya R, Arita K. The New Antiepileptic Drugs: Their Neuropharmacology and Clinical Indications. *Neurol Med Chir (Tokyo)*. May 15 2016;56(5):205-20. doi:10.2176/nmc.ra.2015-0344
37. Simon DW, McGeachy MJ, Bayir H, Clark RS, Loane DJ, Kochanek PM. The far-reaching scope of neuroinflammation after traumatic brain injury. *Nat Rev Neurol*. Mar 2017;13(3):171-191. doi:10.1038/nrneurol.2017.13
38. Corrigan F, Mander KA, Leonard AV, Vink R. Neurogenic inflammation after traumatic brain injury and its potentiation of classical inflammation. *J Neuroinflammation*. Oct 11 2016;13(1):264. doi:10.1186/s12974-016-0738-9
39. Kalra S, Malik R, Singh G, et al. Pathogenesis and management of traumatic brain injury (TBI): role of neuroinflammation and anti-inflammatory drugs. *Inflammopharmacology*. Aug 2022;30(4):1153-1166. doi:10.1007/s10787-022-01017-8
40. Smith C, Gentleman SM, Leclercq PD, et al. The neuroinflammatory response in humans after traumatic brain injury. *Neuropathol Appl Neurobiol*. Oct 2013;39(6):654-66. doi:10.1111/nan.12008

41. Whitney K, Nikulina E, Rahman SN, Alexis A, Bergold PJ. Delayed dosing of minocycline plus N-acetylcysteine reduces neurodegeneration in distal brain regions and restores spatial memory after experimental traumatic brain injury. *Exp Neurol*. Nov 2021;345:113816. doi:10.1016/j.expneurol.2021.113816
42. Rana A, Singh S, Deshmukh R, Kumar A. Pharmacological potential of tocopherol and doxycycline against traumatic brain injury-induced cognitive/motor impairment in rats. *Brain Inj*. Jul 2 2020;34(8):1039-1050. doi:10.1080/02699052.2020.1772508
43. Haber M, Abdel Baki SG, Grin'kina NM, et al. Minocycline plus N-acetylcysteine synergize to modulate inflammation and prevent cognitive and memory deficits in a rat model of mild traumatic brain injury. *Exp Neurol*. Nov 2013;249:169-77. doi:10.1016/j.expneurol.2013.09.002
44. Haber M, James J, Kim J, et al. Minocycline plus N-acteylcysteine induces remyelination, synergistically protects oligodendrocytes and modifies neuroinflammation in a rat model of mild traumatic brain injury. *J Cereb Blood Flow Metab*. Aug 2018;38(8):1312-1326. doi:10.1177/0271678X17718106
45. Sangobowale M, Nikulina E, Bergold PJ. Minocycline plus N-acetylcysteine protect oligodendrocytes when first dosed 12 hours after closed head injury in mice. *Neurosci Lett*. Aug 24 2018;682:16-20. doi:10.1016/j.neulet.2018.06.010
46. Campolo M, Ahmad A, Crupi R, et al. Combination therapy with melatonin and dexamethasone in a mouse model of traumatic brain injury. *J Endocrinol*. Jun 2013;217(3):291-301. doi:10.1530/JOE-13-0022
47. Thal SC, Schaible EV, Neuhaus W, et al. Inhibition of proteasomal glucocorticoid receptor degradation restores dexamethasone-mediated stabilization of the blood-brain barrier after traumatic brain injury. *Crit Care Med*. May 2013;41(5):1305-15. doi:10.1097/CCM.0b013e31827ca494
48. Ekici MA, Uysal O, Cikriklar HI, et al. Effect of etanercept and lithium chloride on preventing secondary tissue damage in rats with experimental diffuse severe brain injury. *Eur Rev Med Pharmacol Sci*. 2014;18(1):10-27.
49. Webster G, Del Rosso JQ. Anti-inflammatory activity of tetracyclines. *Dermatol Clin*. Apr 2007;25(2):133-5, v. doi:10.1016/j.det.2007.01.012
50. Li J, Jia B, Cheng Y, Song Y, Li Q, Luo C. Targeting Molecular Mediators of Ferroptosis and Oxidative Stress for Neurological Disorders. *Oxid Med Cell Longev*. 2022;2022:3999083. doi:10.1155/2022/3999083
51. Narouiepour A, Ebrahimzadeh-Bideskan A, Rajabzadeh G, Gorji A, Negah SS. Neural stem cell therapy in conjunction with curcumin loaded in niosomal nanoparticles enhanced recovery from traumatic brain injury. *Sci Rep*. Mar 4 2022;12(1):3572. doi:10.1038/s41598-022-07367-1
52. Ghazale H, Ramadan N, Mantash S, et al. Docosahexaenoic acid (DHA) enhances the therapeutic potential of neonatal neural stem cell transplantation post-Traumatic brain injury. *Behav Brain Res*. Mar 15 2018;340:1-13. doi:10.1016/j.bbr.2017.11.007
53. Paradells S, Zipancic I, Martinez-Losa MM, et al. Lipoic acid and bone marrow derived cells therapy induce angiogenesis and cell proliferation after focal brain injury. *Brain Inj*. 2015;29(3):380-95. doi:10.3109/02699052.2014.973448
54. Day NL, Carle MS, Floyd CL. Post-injury administration of a combination of memantine and 17beta-estradiol is protective in a rat model of traumatic brain injury. *Neurochem Int*. Dec 2017;111:57-68. doi:10.1016/j.neuint.2017.04.018
55. Lamprecht MR, Morrison B, 3rd. A Combination Therapy of 17beta-Estradiol and Memantine Is More Neuroprotective Than Monotherapies in an Organotypic Brain Slice Culture Model of Traumatic Brain Injury. *J Neurotrauma*. Sep 1 2015;32(17):1361-8. doi:10.1089/neu.2015.3912
56. Colton K, Yang S, Hu PF, et al. Intracranial pressure response after pharmacologic treatment of intracranial hypertension. *J Trauma Acute Care Surg*. Jul 2014;77(1):47-53; discussion 53. doi:10.1097/TA.0000000000000270
57. Mollica A, Greben R, Oriuwa C, Siddiqi SH, Burke MJ. Neuromodulation Treatments for Mild Traumatic Brain Injury and Post-concussive Symptoms. *Curr Neurol Neurosci Rep*. Mar 2022;22(3):171-181. doi:10.1007/s11910-022-01183-w
58. Surendrakumar S, Rabelo TK, Campos ACP, et al. Neuromodulation Therapies in Pre-Clinical Models of Traumatic Brain Injury: Systematic Review and Translational Applications. *J Neurotrauma*. Sep 23 2022;doi:10.1089/neu.2022.0286
59. Lee MJ, Zhou Y, Greenwald BD. Update on Non-Pharmacological Interventions for Treatment of Post-Traumatic Headache. *Brain Sci*. Oct 6 2022;12(10)doi:10.3390/brainsci12101357
60. Cohen SL, Bikson M, Badran BW, George MS. A visual and narrative timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices. *Brain Stimul*. Jan-Feb 2022;15(1):73-75. doi:10.1016/j.brs.2021.11.010
61. Pink AE, Williams C, Alderman N, Stoffels M. The use of repetitive transcranial magnetic stimulation (rTMS) following traumatic brain injury (TBI): A scoping review. *Neuropsychol Rehabil*. Apr 2021;31(3):479-505. doi:10.1080/09602011.2019.1706585

62. Luo J, Feng Y, Li M, Yin M, Qin F, Hu X. Repetitive Transcranial Magnetic Stimulation Improves Neurological Function and Promotes the Anti-inflammatory Polarization of Microglia in Ischemic Rats. *Front Cell Neurosci*. 2022;16:878345. doi:10.3389/fncel.2022.878345
63. Liang H, Xu C, Hu S, et al. Repetitive Transcranial Magnetic Stimulation Improves Neuropathy and Oxidative Stress Levels in Rats with Experimental Cerebral Infarction through the Nrf2 Signaling Pathway. *Evid Based Complement Alternat Med*. 2021;2021:3908677. doi:10.1155/2021/3908677
64. A Martino Cinnera SB, M Iosa, et al. Clinical effects of non-invasive cerebellar magnetic stimulation treatment combined with neuromotor rehabilitation in traumatic brain injury. A single case study. *Functional Neurology*. 31(2):117-120.
65. Zhou LH, X; Li, H; et al. Rehabilitation effect of rTMS combined with cognitive training on cognitive impairment after traumatic brain injury. *Am J Transl Res*. 2021;13(10):11711-11717.
66. Frasca D, Tomaszczyk J, McFadyen BJ, Green RE. Traumatic brain injury and post-acute decline: what role does environmental enrichment play? A scoping review. *Front Hum Neurosci*. 2013;7:31. doi:10.3389/fnhum.2013.00031
67. Maegele M, Lippert-Gruener M, Ester-Bode T, et al. Multimodal early onset stimulation combined with enriched environment is associated with reduced CNS lesion volume and enhanced reversal of neuromotor dysfunction after traumatic brain injury in rats. *Eur J Neurosci*. May 2005;21(9):2406-18. doi:10.1111/j.1460-9568.2005.04070.x
68. Maegele M, Lippert-Gruener M, Ester-Bode T, et al. Reversal of neuromotor and cognitive dysfunction in an enriched environment combined with multimodal early onset stimulation after traumatic brain injury in rats. *J Neurotrauma*. Jul 2005;22(7):772-82. doi:10.1089/neu.2005.22.772
69. Shin SS, Krishnan V, Stokes W, et al. Transcranial magnetic stimulation and environmental enrichment enhances cortical excitability and functional outcomes after traumatic brain injury. *Brain Stimul*. Nov-Dec 2018;11(6):1306-1313. doi:10.1016/j.brs.2018.07.050
70. Bleimeister IH, Wolff M, Lam TR, et al. Environmental enrichment and amantadine confer individual but nonadditive enhancements in motor and spatial learning after controlled cortical impact injury. *Brain Res*. Jul 1 2019;1714:227-233. doi:10.1016/j.brainres.2019.03.007
71. de la Tremblaye PB, Bondi CO, Lajud N, Cheng JP, Radabaugh HL, Kline AE. Galantamine and Environmental Enrichment Enhance Cognitive Recovery after Experimental Traumatic Brain Injury But Do Not Confer Additional Benefits When Combined. *J Neurotrauma*. Apr 15 2017;34(8):1610-1622. doi:10.1089/neu.2016.4790
72. Monaco CM, Gebhardt KM, Chlebowski SM, et al. A Combined Therapeutic Regimen of Buspirone and Environmental Enrichment Is More Efficacious than Either Alone in Enhancing Spatial Learning in Brain-Injured Pediatric Rats. *Journal of Neurotrauma*. 2014;31(23):1934-1941. doi:10.1089/neu.2014.3541
73. Kline AE, Olsen AS, Sozda CN, Hoffman AN, Cheng JP. Evaluation of a combined treatment paradigm consisting of environmental enrichment and the 5-HT1A receptor agonist buspirone after experimental traumatic brain injury. *J Neurotrauma*. Jul 1 2012;29(10):1960-9. doi:10.1089/neu.2012.2385
74. Yan HQ, Yu J, Kline AE, et al. Evaluation of combined fibroblast growth factor-2 and moderate hypothermia therapy in traumatically brain injured rats. *Brain Res*. Dec 22 2000;887(1):134-43. doi:10.1016/s0006-8993(00)03002-x
75. Song B, Wang XX, Yang HY, Kong LT, Sun HY. Temperature-sensitive bone mesenchymal stem cells combined with mild hypothermia reduces neurological deficit in rats of severe traumatic brain injury. *Brain Inj*. Jun 6 2020;34(7):975-982. doi:10.1080/02699052.2020.1753112
76. Sinha S, Raheja A, Samson N, et al. A randomized placebo-controlled trial of progesterone with or without hypothermia in patients with acute severe traumatic brain injury. *Neurol India*. Nov-Dec 2017;65(6):1304-1311. doi:10.4103/0028-3886.217973
77. Jacotte-Simancas A, Costa-Miserachs D, Coll-Andreu M, Torras-Garcia M, Borlongan CV, Portell-Cortes I. Effects of voluntary physical exercise, citicoline, and combined treatment on object recognition memory, neurogenesis, and neuroprotection after traumatic brain injury in rats. *J Neurotrauma*. May 15 2015;32(10):739-51. doi:10.1089/neu.2014.3502
78. Yao X, Wang W, Li Y, et al. Study of the mechanism by which MSCs combined with LITUS treatment improve cognitive dysfunction caused by traumatic brain injury. *Neurosci Lett*. Sep 14 2022;787:136825. doi:10.1016/j.neulet.2022.136825
79. Lindblad C, Raj R, Zeiler FA, Thelin EP. Current state of high-fidelity multimodal monitoring in traumatic brain injury. *Acta Neurochir (Wien)*. Dec 2022;164(12):3091-3100. doi:10.1007/s00701-022-05383-8
80. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Indications for intracranial pressure monitoring. *J Neurotrauma*. Jun-Jul 2000;17(6-7):479-91. doi:10.1089/neu.2000.17.479
81. Petkus V, Preiksaitis A, Chaleckas E, et al. Optimal Cerebral Perfusion Pressure: Targeted Treatment for Severe Traumatic Brain Injury. *J Neurotrauma*. Jan 15 2020;37(2):389-396. doi:10.1089/neu.2019.6551

82. Casault C, Couillard P, Kromm J, Rosenthal E, Kramer A, Brindley P. Multimodal brain monitoring following traumatic brain injury: A primer for intensive care practitioners. *J Intensive Care Soc*. May 2022;23(2):191-202. doi:10.1177/1751143720980273
83. Robinson MB, Shin P, Alunday R, Cole C, Torbey MT, Carlson AP. Decision-making for decompressive craniectomy in traumatic brain injury aided by multimodality monitoring: illustrative case. *J Neurosurg Case Lessons*. Jun 21 2021;1(25):CASE2197. doi:10.3171/CASE2197
84. Young AM, Donnelly J, Czosnyka M, et al. Continuous Multimodality Monitoring in Children after Traumatic Brain Injury-Preliminary Experience. *PLoS One*. 2016;11(3):e0148817. doi:10.1371/journal.pone.0148817
85. Sykora M, Czosnyka M, Liu X, et al. Autonomic Impairment in Severe Traumatic Brain Injury: A Multimodal Neuromonitoring Study. *Crit Care Med*. Jun 2016;44(6):1173-81. doi:10.1097/CCM.0000000000001624
86. Lang SS, Kumar NK, Zhao C, et al. Invasive brain tissue oxygen and intracranial pressure (ICP) monitoring versus ICP-only monitoring in pediatric severe traumatic brain injury. *J Neurosurg Pediatr*. May 27 2022:1-11. doi:10.3171/2022.4.PEDS21568
87. Okonkwo DO, Shutter LA, Moore C, et al. Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial. *Crit Care Med*. Nov 2017;45(11):1907-1914. doi:10.1097/CCM.0000000000002619
88. Dellazizzo L, Demers SP, Charbonney E, et al. Minimal PaO2 threshold after traumatic brain injury and clinical utility of a novel brain oxygenation ratio. *J Neurosurg*. Nov 2 2018:1-9. doi:10.3171/2018.5.JNS18651
89. Venturini S, Bhatti F, Timofeev I, et al. Microdialysis-Based Classifications of Abnormal Metabolic States after Traumatic Brain Injury: A Systematic Review of the Literature. *J Neurotrauma*. Nov 7 2022;doi:10.1089/neu.2021.0502
90. Marini CP, Stoller C, McNelis J, Del Deo V, Prabhakaran K, Petrone P. Correlation of brain flow variables and metabolic crisis: a prospective study in patients with severe traumatic brain injury. *Eur J Trauma Emerg Surg*. Feb 2022;48(1):537-544. doi:10.1007/s00068-020-01447-5
91. Isa R, Wan Adnan WA, Ghazali G, et al. Outcome of severe traumatic brain injury: comparison of three monitoring approaches. *Neurosurg Focus*. Dec 15 2003;15(6):E1. doi:10.3171/foc.2003.15.6.1
92. Khellaf A, Garcia NM, Tajsic T, et al. Focally administered succinate improves cerebral metabolism in traumatic brain injury patients with mitochondrial dysfunction. *J Cereb Blood Flow Metab*. Jan 2022;42(1):39-55. doi:10.1177/0271678X211042112
93. Khellaf A, Khan DZ, Helmy A. Recent advances in traumatic brain injury. *J Neurol*. Nov 2019;266(11):2878-2889. doi:10.1007/s00415-019-09541-4
94. Abdul-Muneer PM, Chandra N, Haorah J. Interactions of oxidative stress and neurovascular inflammation in the pathogenesis of traumatic brain injury. *Mol Neurobiol*. 2015;51(3):966-79. doi:10.1007/s12035-014-8752-3
95. Reddi S, Thakker-Varia S, Alder J, Giarratana AO. Status of precision medicine approaches to traumatic brain injury. *Neural Regen Res*. Oct 2022;17(10):2166-2171. doi:10.4103/1673-5374.335824
96. Unterberg AW, Kiening KL, Hartl R, Bardt T, Sarrafzadeh AS, Lanksch WR. Multimodal monitoring in patients with head injury: evaluation of the effects of treatment on cerebral oxygenation. *J Trauma*. May 1997;42(5 Suppl):S32-7. doi:10.1097/00005373-199705001-00006
97. Thapa K, Khan H, Singh TG, Kaur A. Traumatic Brain Injury: Mechanistic Insight on Pathophysiology and Potential Therapeutic Targets. *J Mol Neurosci*. Sep 2021;71(9):1725-1742. doi:10.1007/s12031-021-01841-7
98. Yilmaz C, Karali K, Fodelianaki G, et al. Neurosteroids as regulators of neuroinflammation. *Front Neuroendocrinol*. Oct 2019;55:100788. doi:10.1016/j.yfrne.2019.100788
99. Gupte R, Brooks W, Vukas R, Pierce J, Harris J. Sex Differences in Traumatic Brain Injury: What We Know and What We Should Know. *J Neurotrauma*. Nov 15 2019;36(22):3063-3091. doi:10.1089/neu.2018.6171
100. Inampudi C, Ciccotosto GD, Cappai R, Crack PJ. Genetic Modulators of Traumatic Brain Injury in Animal Models and the Impact of Sex-Dependent Effects. *J Neurotrauma*. Mar 1 2020;37(5):706-723. doi:10.1089/neu.2019.6955
101. Doran SJ, Ritzel RM, Glaser EP, Henry RJ, Faden AI, Loane DJ. Sex Differences in Acute Neuroinflammation after Experimental Traumatic Brain Injury Are Mediated by Infiltrating Myeloid Cells. *J Neurotrauma*. Apr 1 2019;36(7):1040-1053. doi:10.1089/neu.2018.6019
102. Scott MC, Prabhakara KS, Walters AJ, Olson SD, Cox CS, Jr. Determining Sex-Based Differences in Inflammatory Response in an Experimental Traumatic Brain Injury Model. *Front Immunol*. 2022;13:753570. doi:10.3389/fimmu.2022.753570
103. Lazarus RC, Buonora JE, Jacobowitz DM, Mueller GP. Protein carbonylation after traumatic brain injury: cell specificity, regional susceptibility, and gender differences. *Free Radic Biol Med*. Jan 2015;78:89-100. doi:10.1016/j.freeradbiomed.2014.10.507

104. Khaksari M, Soltani Z, Shahrokhi N. Effects of Female Sex Steroids Administration on Pathophysiologic Mechanisms in Traumatic Brain Injury. *Transl Stroke Res*. Aug 2018;9(4):393-416. doi:10.1007/s12975-017-0588-5
105. Khaksari M, Soltani Z, Shahrokhi N, Moshtaghi G, Asadikaram G. The role of estrogen and progesterone, administered alone and in combination, in modulating cytokine concentration following traumatic brain injury. *Can J Physiol Pharmacol*. Jan 2011;89(1):31-40. doi:10.1139/y10-103
106. Tang H, Hua F, Wang J, et al. Progesterone and vitamin D combination therapy modulates inflammatory response after traumatic brain injury. *Brain Inj*. Sep 2015;29(10):1165-1174. doi:10.3109/02699052.2015.1035330
107. von Oettingen G, Bergholt B, Gyldensted C, Astrup J. Blood flow and ischemia within traumatic cerebral contusions. *Neurosurgery*. Apr 2002;50(4):781-8; discussion 788-90. doi:10.1097/00006123-200204000-00019
108. Kawai N, Nakamura T, Tamiya T, Nagao S. Metabolic disturbance without brain ischemia in traumatic brain injury: a positron emission tomography study. *Acta Neurochir Suppl*. 2008;102:241-5. doi:10.1007/978-3-211-85578-2_46
109. Harish G, Mahadevan A, Pruthi N, et al. Characterization of traumatic brain injury in human brains reveals distinct cellular and molecular changes in contusion and pericontusion. *J Neurochem*. Jul 2015;134(1):156-72. doi:10.1111/jnc.13082
110. Rhodes JK. Actions of glucocorticoids and related molecules after traumatic brain injury. *Curr Opin Crit Care*. Apr 2003;9(2):86-91. doi:10.1097/00075198-200304000-00002
111. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*. Oct 9-15 2004;364(9442):1321-8. doi:10.1016/S0140-6736(04)17188-2
112. Chen JH, Xu YN, Ji M, Li PP, Yang LK, Wang YH. Multimodal monitoring combined with hypothermia for the management of severe traumatic brain injury: A case report. *Exp Ther Med*. May 2018;15(5):4253-4258. doi:10.3892/etm.2018.5994
113. Sun HT, Zheng M, Wang Y, Diao Y, Zhao W, Wei Z. Monitoring intracranial pressure utilizing a novel pattern of brain multiparameters in the treatment of severe traumatic brain injury. *Neuropsychiatr Dis Treat*. 2016;12:1517-23. doi:10.2147/NDT.S106915
114. Yan C, Mao J, Yao C, Liu Y, Yan H, Jin W. Neuroprotective effects of mild hypothermia against traumatic brain injury by the involvement of the Nrf2/ARE pathway. *Brain Behav*. Aug 2022;12(8):e2686. doi:10.1002/brb3.2686
115. Baillieul S, Chacaroun S, Doutreleau S, Detante O, Pepin JL, Verges S. Hypoxic conditioning and the central nervous system: A new therapeutic opportunity for brain and spinal cord injuries? *Exp Biol Med (Maywood)*. Jun 2017;242(11):1198-1206. doi:10.1177/1535370217712691
116. Lu M, Wang Y, Yin X, Li Y, Li H. Cerebral protection by remote ischemic post-conditioning in patients with ischemic stroke: A systematic review and meta-analysis of randomized controlled trials. *Front Neurol*. 2022;13:905400. doi:10.3389/fneur.2022.905400
117. Torres-Querol C, Quintana-Luque M, Arque G, Purroy F. Preclinical evidence of remote ischemic conditioning in ischemic stroke, a metanalysis update. *Sci Rep*. Dec 9 2021;11(1):23706. doi:10.1038/s41598-021-03003-6
118. Sandweiss AJ, Azim A, Ibraheem K, et al. Remote ischemic conditioning preserves cognition and motor coordination in a mouse model of traumatic brain injury. *J Trauma Acute Care Surg*. Dec 2017;83(6):1074-1081. doi:10.1097/TA.0000000000001626
119. Pandit V, Khan M, Zakaria ER, et al. Continuous remote ischemic conditioning attenuates cognitive and motor deficits from moderate traumatic brain injury. *J Trauma Acute Care Surg*. Jul 2018;85(1):48-53. doi:10.1097/TA.0000000000001835
120. Drew KL, Rice ME, Kuhn TB, Smith MA. Neuroprotective adaptations in hibernation: therapeutic implications for ischemia-reperfusion, traumatic brain injury and neurodegenerative diseases. *Free Radic Biol Med*. Sep 1 2001;31(5):563-73. doi:10.1016/s0891-5849(01)00628-1
121. Singhal NS, Sun CH, Lee EM, Ma DK. Resilience to Injury: A New Approach to Neuroprotection? *Neurotherapeutics*. Apr 2020;17(2):457-474. doi:10.1007/s13311-020-00832-7
122. Hirst TC, Klasen MG, Rhodes JK, Macleod MR, Andrews PJD. A Systematic Review and Meta-Analysis of Hypothermia in Experimental Traumatic Brain Injury: Why Have Promising Animal Studies Not Been Replicated in Pragmatic Clinical Trials? *J Neurotrauma*. Oct 1 2020;37(19):2057-2068. doi:10.1089/neu.2019.6923
123. Chen H, Wu F, Yang P, Shao J, Chen Q, Zheng R. A meta-analysis of the effects of therapeutic hypothermia in adult patients with traumatic brain injury. *Crit Care*. Dec 5 2019;23(1):396. doi:10.1186/s13054-019-2667-3
124. Zhao WY, Chen SB, Wang JJ, et al. Establishment of an ideal time window model in hypothermic-targeted temperature management after traumatic brain injury in rats. *Brain Res*. Aug 15 2017;1669:141-149. doi:10.1016/j.brainres.2017.06.006

125. Feng JZ, Wang WY, Zeng J, et al. Optimization of brain metabolism using metabolic-targeted therapeutic hypothermia can reduce mortality from traumatic brain injury. *J Trauma Acute Care Surg*. Aug 2017;83(2):296-304. doi:10.1097/TA.0000000000001522
126. Lapi D, Scuri R, Colantuoni A. Trigeminal Cardiac Reflex and Cerebral Blood Flow Regulation. *Front Neurosci*. 2016;10:470. doi:10.3389/fnins.2016.00470
127. Sureda A, Batle JM, Tur JA, Pons A. Competitive apnea diving sessions induces an adaptative antioxidant response in mononucleated blood cells. *J Physiol Biochem*. Sep 2015;71(3):373-80. doi:10.1007/s13105-015-0417-9
128. Bulmer AC, Coombes JS, Sharman JE, Stewart IB. Effects of maximal static apnea on antioxidant defenses in trained free divers. *Med Sci Sports Exerc*. Jul 2008;40(7):1307-13. doi:10.1249/MSS.0b013e31816a7188
129. Elia A, Gennser M, Harlow PS, Lees MJ. Physiology, pathophysiology and (mal)adaptations to chronic apnoeic training: a state-of-the-art review. *Eur J Appl Physiol*. Jun 2021;121(6):1543-1566. doi:10.1007/s00421-021-04664-x
130. Eftedal I, Flatberg A, Drvis I, Dujic Z. Immune and inflammatory responses to freediving calculated from leukocyte gene expression profiles. *Physiol Genomics*. Nov 1 2016;48(11):795-802. doi:10.1152/physiolgenomics.00048.2016
131. Bagchi A, Batten AJ, Levin M, et al. Intrinsic anti-inflammatory properties in the serum of two species of deep-diving seal. *J Exp Biol*. Jul 9 2018;221(Pt 13)doi:10.1242/jeb.178491
132. Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. May 25 2000;405(6785):458-62. doi:10.1038/35013070
133. Tracey KJ. The inflammatory reflex. *Nature*. Dec 19-26 2002;420(6917):853-9. doi:10.1038/nature01321
134. Shah SA, Lowder RJ, Kuceyeski A. Quantitative multimodal imaging in traumatic brain injuries producing impaired cognition. *Curr Opin Neurol*. Dec 2020;33(6):691-698. doi:10.1097/WCO.0000000000000872
135. Shi J, Teng J, Du X, Li N. Multi-Modal Analysis of Resting-State fMRI Data in mTBI Patients and Association With Neuropsychological Outcomes. *Front Neurol*. 2021;12:639760. doi:10.3389/fneur.2021.639760
136. Dean PJ, Sato JR, Vieira G, McNamara A, Sterr A. Multimodal imaging of mild traumatic brain injury and persistent postconcussion syndrome. *Brain Behav*. Jan 2015;5(1):45-61. doi:10.1002/brb3.292
137. Lunkova E, Guberman GI, Ptito A, Saluja RS. Noninvasive magnetic resonance imaging techniques in mild traumatic brain injury research and diagnosis. *Hum Brain Mapp*. Nov 2021;42(16):5477-5494. doi:10.1002/hbm.25630
138. Lippa SM, Yeh PH, Ollinger J, Brickell TA, French LM, Lange RT. White Matter Integrity Relates to Cognition in Service Members and Veterans after Complicated Mild, Moderate, and Severe Traumatic Brain Injury, But Not Uncomplicated Mild Traumatic Brain Injury. *J Neurotrauma*. Oct 18 2022;doi:10.1089/neu.2022.0276
139. Zhang J, Zhang H, Yan F, et al. Investigating the mechanism and prognosis of patients with disorders of consciousness on the basis of brain networks between the thalamus and whole-brain. *Front Neurol*. 2022;13:990686. doi:10.3389/fneur.2022.990686
140. Liu Y, Lu L, Li F, Chen YC. Neuropathological Mechanisms of Mild Traumatic Brain Injury: A Perspective From Multimodal Magnetic Resonance Imaging. *Front Neurosci*. 2022;16:923662. doi:10.3389/fnins.2022.923662
141. Harris NG, Paydar A, Smith GS, Lepore S. Diffusion MR imaging acquisition and analytics for microstructural delineation in pre-clinical models of TBI. *J Neurosci Res*. May 2022;100(5):1128-1139. doi:10.1002/jnr.24416
142. Minchew HM, Ferren SL, Christian SK, et al. Comparing imaging biomarkers of cerebral edema after TBI in young adult male and female rats. *Brain Res*. Aug 15 2022;1789:147945. doi:10.1016/j.brainres.2022.147945
143. Mayer AR, Bellgowan PS, Hanlon FM. Functional magnetic resonance imaging of mild traumatic brain injury. *Neurosci Biobehav Rev*. Feb 2015;49:8-18. doi:10.1016/j.neubiorev.2014.11.016
144. Storti SF, Formaggio E, Franchini E, et al. A multimodal imaging approach to the evaluation of post-traumatic epilepsy. *MAGMA*. Oct 2012;25(5):345-60. doi:10.1007/s10334-012-0316-9
145. French JA, Bebin M, Dichter MA, et al. Antiepileptogenesis and disease modification: Clinical and regulatory issues. *Epilepsia Open*. Sep 2021;6(3):483-492. doi:10.1002/epi4.12526
146. Stovell MG, Yan JL, Sleigh A, et al. Assessing Metabolism and Injury in Acute Human Traumatic Brain Injury with Magnetic Resonance Spectroscopy: Current and Future Applications. *Front Neurol*. 2017;8:426. doi:10.3389/fneur.2017.00426
147. Kulkarni P, Morrison TR, Cai X, et al. Neuroradiological Changes Following Single or Repetitive Mild TBI. *Front Syst Neurosci*. 2019;13:34. doi:10.3389/fnsys.2019.00034
148. Harris JL, Yeh HW, Choi IY, et al. Altered neurochemical profile after traumatic brain injury: (1)H-MRS biomarkers of pathological mechanisms. *J Cereb Blood Flow Metab*. Dec 2012;32(12):2122-34. doi:10.1038/jcbfm.2012.114

149. Yasmin A, Pitkanen A, Jokivarsi K, Poutiainen P, Grohn O, Immonen R. MRS Reveals Chronic Inflammation in T2w MRI-Negative Perilesional Cortex - A 6-Months Multimodal Imaging Follow-Up Study. *Front Neurosci*. 2019;13:863. doi:10.3389/fnins.2019.00863
150. Wong SW, Vivash L, Mudududdla R, et al. Development of [(18)F]MIPS15692, a radiotracer with in vitro proof-of-concept for the imaging of MER tyrosine kinase (MERTK) in neuroinflammatory disease. *Eur J Med Chem*. Dec 15 2021;226:113822. doi:10.1016/j.ejmech.2021.113822
151. Zeiler FA, Iturria-Medina Y, Thelin EP, et al. Integrative Neuroinformatics for Precision Prognostication and Personalized Therapeutics in Moderate and Severe Traumatic Brain Injury. *Front Neurol*. 2021;12:729184. doi:10.3389/fneur.2021.729184
152. Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery*. Dec 2005;57(6):1173-82; discussion 1173-82. doi:10.1227/01.neu.0000186013.63046.6b
153. Raj R, Siironen J, Skrifvars MB, Hernesniemi J, Kivisaari R. Predicting outcome in traumatic brain injury: development of a novel computerized tomography classification system (Helsinki computerized tomography score). *Neurosurgery*. Dec 2014;75(6):632-46; discussion 646-7. doi:10.1227/NEU.0000000000000533
154. Sheth KN, Mazurek MH, Yuen MM, et al. Assessment of Brain Injury Using Portable, Low-Field Magnetic Resonance Imaging at the Bedside of Critically Ill Patients. *JAMA Neurol*. Sep 8 2020;78(1):41-7. doi:10.1001/jamaneurol.2020.3263
155. Turpin J, Unadkat P, Thomas J, et al. Portable Magnetic Resonance Imaging for ICU Patients. *Crit Care Explor*. Dec 2020;2(12):e0306. doi:10.1097/CCE.0000000000000306
156. Palacios EM, Yuh EL, Mac Donald CL, et al. Diffusion Tensor Imaging Reveals Elevated Diffusivity of White Matter Microstructure that Is Independently Associated with Long-Term Outcome after Mild Traumatic Brain Injury: A TRACK-TBI Study. *J Neurotrauma*. Oct 2022;39(19-20):1318-1328. doi:10.1089/neu.2021.0408
157. Mohamed M, Alamri A, Mohamed M, et al. Prognosticating outcome using magnetic resonance imaging in patients with moderate to severe traumatic brain injury: a machine learning approach. *Brain Inj*. Feb 23 2022;36(3):353-358. doi:10.1080/02699052.2022.2034184
158. Vergara VM, Mayer AR, Damaraju E, Kiehl KA, Calhoun V. Detection of Mild Traumatic Brain Injury by Machine Learning Classification Using Resting State Functional Network Connectivity and Fractional Anisotropy. *J Neurotrauma*. Mar 1 2017;34(5):1045-1053. doi:10.1089/neu.2016.4526
159. Daley M, Cameron S, Ganesan SL, et al. Pediatric severe traumatic brain injury mortality prediction determined with machine learning-based modeling. *Injury*. Mar 2022;53(3):992-998. doi:10.1016/j.injury.2022.01.008
160. Hoffman H, Abi-Aad K, Bunch KM, Beutler T, Otite FO, Chin LS. Outcomes associated with brain tissue oxygen monitoring in patients with severe traumatic brain injury undergoing intracranial pressure monitoring. *J Neurosurg*. May 14 2021;135(6):1799-1806. doi:10.3171/2020.11.JNS203739
161. Luca L, Rogobete AF, Bedreag OH, et al. Intracranial Pressure Monitoring as a Part of Multimodal Monitoring Management of Patients with Critical Polytrauma: Correlation between Optimised Intensive Therapy According to Intracranial Pressure Parameters and Clinical Picture. *Turk J Anaesthesiol Reanim*. Dec 2015;43(6):412-7. doi:10.5152/TJAR.2015.56933
162. Andrew RD, Hartings JA, Ayata C, et al. The Critical Role of Spreading Depolarizations in Early Brain Injury: Consensus and Contention. *Neurocrit Care*. Jun 2022;37(Suppl 1):83-101. doi:10.1007/s12028-021-01431-w
163. Hinzman JM, Andaluz N, Shutter LA, et al. Inverse neurovascular coupling to cortical spreading depolarizations in severe brain trauma. *Brain*. Nov 2014;137(Pt 11):2960-72. doi:10.1093/brain/awu241
164. Sueiras M, Thonon V, Santamarina E, et al. Is Spreading Depolarization a Risk Factor for Late Epilepsy? A Prospective Study in Patients with Traumatic Brain Injury and Malignant Ischemic Stroke Undergoing Decompressive Craniectomy. *Neurocrit Care*. Jun 2021;34(3):876-888. doi:10.1007/s12028-020-01107-x
165. Andrew RD, Farkas E, Hartings JA, et al. Questioning Glutamate Excitotoxicity in Acute Brain Damage: The Importance of Spreading Depolarization. *Neurocrit Care*. Jun 2022;37(Suppl 1):11-30. doi:10.1007/s12028-021-01429-4
166. Rueda Carrillo L, Garcia KA, Yalcin N, Shah M. Ketamine and Its Emergence in the Field of Neurology. *Cureus*. Jul 2022;14(7):e27389. doi:10.7759/cureus.27389
167. Sanchez-Porras R, Kentar M, Zerelles R, et al. Eighteen-hour inhibitory effect of s-ketamine on potassium- and ischemia-induced spreading depolarizations in the gyrencephalic swine brain. *Neuropharmacology*. Sep 15 2022;216:109176. doi:10.1016/j.neuropharm.2022.109176
168. Podell J, Pergakis M, Yang S, et al. Leveraging Continuous Vital Sign Measurements for Real-Time Assessment of Autonomic Nervous System Dysfunction After Brain Injury: A Narrative Review of Current and Future Applications. *Neurocrit Care*. Aug 2022;37(Suppl 2):206-219. doi:10.1007/s12028-022-01491-6

169. Rajagopalan S, Baker W, Mahanna-Gabrielli E, Kofke AW, Balu R. Hierarchical Cluster Analysis Identifies Distinct Physiological States After Acute Brain Injury. *Neurocrit Care*. Apr 2022;36(2):630-639. doi:10.1007/s12028-021-01362-6
170. Lazaridis C, Ajith A, Mansour A, Okonkwo DO, Diaz-Arrastia R, Mayampurath A. Prediction of Intracranial Hypertension and Brain Tissue Hypoxia Utilizing High-Resolution Data from the BOOST-II Clinical Trial. *Neurotrauma Rep*. 2022;3(1):473-478. doi:10.1089/neur.2022.0055
171. Wilde EA, Wanner IB, Kenney K, et al. A Framework to Advance Biomarker Development in the Diagnosis, Outcome Prediction, and Treatment of Traumatic Brain Injury. *J Neurotrauma*. Apr 2022;39(7-8):436-457. doi:10.1089/neu.2021.0099
172. Jones S, Schwartzbauer G, Jia X. Brain Monitoring in Critically Neurologically Impaired Patients. *Int J Mol Sci*. Dec 27 2016;18(1)doi:10.3390/ijms18010043
173. Seule M, Sikorski C, Sakowitz O, et al. Evaluation of a New Brain Tissue Probe for Intracranial Pressure, Temperature, and Cerebral Blood Flow Monitoring in Patients with Aneurysmal Subarachnoid Hemorrhage. *Neurocrit Care*. Oct 2016;25(2):193-200. doi:10.1007/s12028-016-0284-4
174. Appavu B, Burrows BT, Nickoles T, et al. Implementation of Multimodality Neurologic Monitoring Reporting in Pediatric Traumatic Brain Injury Management. *Neurocrit Care*. Aug 2021;35(1):3-15. doi:10.1007/s12028-021-01190-8
175. Pease M, Nwachuku E, Goldschmidt E, Elmer J, Okonkwo DO. Complications from Multimodal Monitoring Do not Affect Long-Term Outcomes in Severe Traumatic Brain Injury. *World Neurosurg*. May 2022;161:e109-e117. doi:10.1016/j.wneu.2022.01.059
176. Robba C, Pozzebon S, Moro B, Vincent JL, Creteur J, Taccone FS. Multimodal non-invasive assessment of intracranial hypertension: an observational study. *Crit Care*. Jun 26 2020;24(1):379. doi:10.1186/s13054-020-03105-z
177. Zeiler FA, Ziesmann MT, Goeres P, et al. A unique method for estimating the reliability learning curve of optic nerve sheath diameter ultrasound measurement. *Crit Ultrasound J*. Dec 2016;8(1):9. doi:10.1186/s13089-016-0044-x
178. Butts C, Wilson J, Lasseigne L, Oral E, Kaban N. Ultrasound of the Optic Nerve Does Not Appear to Be a Consistently Reliable or Generalizable Method to Monitor Changes in Intracranial Pressure. *J Intensive Care Med*. May 2022;37(5):663-670. doi:10.1177/08850666211021737