

Review

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Review

Navigating the Complexities of Traumatic Encephalopathy Syndrome (TES): Current State and Future Challenges

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Abstract: Chronic traumatic encephalopathy (CTE) is a unique neurodegenerative disease that is associated with repetitive head impacts (RHI) in both civilian and military settings. In 2014, the research criteria for the clinical manifestation of CTE, traumatic encephalopathy syndrome (TES) were proposed to improve the clinical identification and understanding of the complex neuropathological phenomena underlying CTE. This review provides a comprehensive overview of the current understanding of the neuropathological and clinical features of CTE, proposed biomarkers of traumatic brain injury (TBI) in both research and clinical settings, and a range of treatments based on previous preclinical and clinical research studies. Due to the heterogeneity of TBI, there is no universally agreed-upon serum, CSF, or neuroimaging marker for its diagnosis. However, as our understanding of this complex disease continues to evolve, it is likely that there will be more robust, early diagnostic methods and effective clinical treatments. This is especially important given the increasing evidence of a correlation between TBI and neurodegenerative conditions, such as Alzheimer's disease and CTE¹. As public awareness of these conditions grows, it is imperative to prioritize both basic and clinical research, as well as the implementation of necessary safe and preventative measures.

Keywords: chronic traumatic encephalopathy (CTE); Alzheimer's disease (AD); traumatic encephalopathy syndrome (TES); traumatic brain injury (TBI); repetitive head impacts (RHI)

1. Background

Chronic traumatic encephalopathy (CTE) is a distinct neurodegenerative disease and often associated with a history of repetitive head impacts (RHI) in the context of sports or combat settings. The defining neuropathological characteristic of CTE includes hyperphosphorylated tau at the depths of cortical sulci and peri-vascular regions². CTE was first reported in a group of boxers, who were described as "punch drunk" by Martland in 1928. His report was focused on a group of boxers who had suffered repetitive head blows throughout their sporting careers, with clinical presentations of both psychiatric symptoms as well as severe memory and neurocognitive deficits, similar to typical dementia patients³. The disease nomenclature evolved into "dementia pugilistica"⁴, and finally CTE in 1949⁵. Renewed interest in CTE began when Omalu et al. reported finding evidence of CTE in three retired football players^{6,7,8}. McKee reported similar findings in three new individuals when reviewing the world literature on CTE including one football player, followed by numerous reports and case studies of evidence of CTE in athletes, veterans, and others exposed to repetitive head trauma.

In 2014, research diagnostic criteria for traumatic encephalopathy syndrome (TES) were proposed for use in clinical research settings to diagnose CTE while alive by Montenigro et al.⁹. They proposed five general criterion for diagnosis of TES, which included (1) a history of multiple head impacts, (2) no other neurological disorders accounting for all the clinical features, (3) clinical features present for a minimum of 12 months, (4) at least one core clinical feature must be present, and (5) the presence of at least two supportive features.

The core features included cognitive deficits, behavioral symptoms, and mood symptoms. The cognitive symptoms, supported by detailed neuropsychological assessments, included changes in

episodic memory, executive function, and attention, as defined by 1.5 standard deviations below normal. Behavioral symptoms included verbal or physical aggression, while mood symptoms included feeling depressed or hopeless. The supportive features included impulsivity, anxiety, apathy, paranoia, suicidality, headache, motor signs including dysarthria and dysgraphia, documented decline, as well as a delayed onset.

The validity of TES was assessed by Mez at al.¹⁰ who examined a total of 336 brain donors exposed to repetitive head impacts in the setting of contact sports, military service, and/or physical violence. A total of 309 donors were diagnosed with TES, with 244 donors with CTE pathology. The TES criterion had measured sensitivity and specificity of 0.97 and 0.21, respectively¹⁰. Hence, TES criterion laid a solid foundation for ruling out CTE pathology but provided limited evidence for ruling in CTE pathology. Having cognitive symptoms was significantly associated with having CTE pathology; by augmenting the TES criteria to require cognitive symptoms, specificity improved (0.48) with limited reduction in sensitivity (0.90). Among older donors (age ≥ 60 years), if AD pathology was present, accuracy of a TES diagnosis was markedly reduced. Furthermore, when the diagnosis of AD was excluded, specificity increased from 0.21 to 0.40, with an acceptable reduction in sensitivity from 0.95 to 0.82. Nonetheless, CTE pathology frequently occurred among those with AD pathology. The authors found that having cognitive symptoms was significantly associated with CTE pathology, increasing the odds by 3.6-fold.

This review endeavors to offer a comprehensive exploration of the underlying pathophysiological mechanisms of traumatic encephalopathy syndrome (TES) and chronic traumatic encephalopathy (CTE). Additionally, it provides an in-depth survey of the present neuroimaging and plasma biomarkers employed in the diagnosis of traumatic brain injury (TBI). Furthermore, it scrutinizes the currently utilized clinical regimens in TBI treatment (refer to Figure 1). Given the rapid evolution of the research field concerning TES, CTE, and TBI at large, this review aims to encapsulate some of the most promising trajectories in the field¹¹.

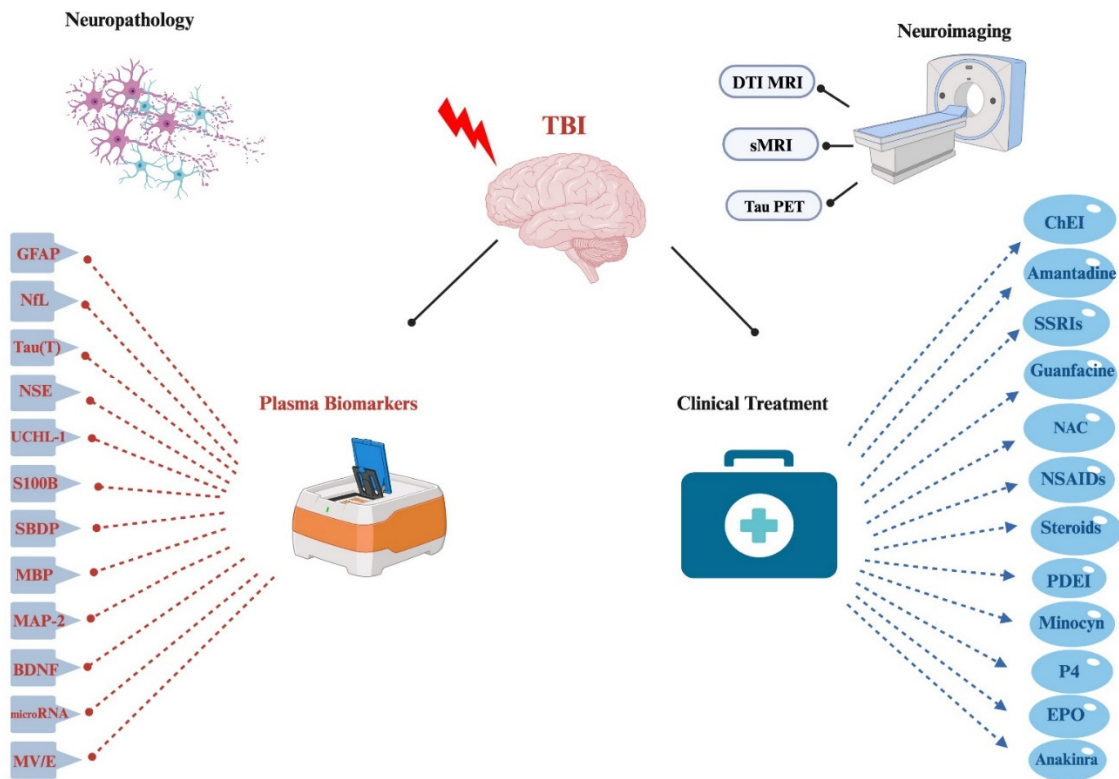


Figure 1. Schematic illustration of major plasma markers of TBI including GFAP (Glial Fibrillary Acidic Protein), NFL (Neurofibrillary light chain), total tau, NSE (Neuron Specific Enolase), UCHL-1 (Ubiquitin C-terminal hydrolase-1), S100B, SBDP (Spectrin Breakdown Products), MBP (Myelin Basic Protein), MAP-2 (Microtubule-Associated Protein-2), BDNF (Brain Derived Neurotrophic Factor),

microRNA, and MV/E (microvesicles and exosomes). Also included are the major clinical treatment options used in treatment of TBI patients, including cholinesterase inhibitors (ChEI), NMDA receptor antagonist (Amantadine), SSRIs, guanfacine, NSAIDs, Nutraceuticals such as NAC, phosphodiesterase inhibitor (PDEI), Minocycline (Minocyn), glucocorticoids and progesterone (P4), Erythropoietin (EPO) and Anakinra. Some of the current promising neuroimaging tools for clinical TBI patients include diffusion tensor imaging (DTI) imaging, structural MRI with corresponding volumetric analysis, as well as Tau PET imaging. Images created with BioRender.com.

2. Neuropathology

In 1973, Corsellis et al.¹² examined 15 boxers with dementia pugilistica and described the neuropathologic substrate of CTE as involving (1) neurofibrillary tangles (NFTs) in the absence of plaques, particularly involving the medial temporal lobe and brainstem tegmentum, (2) neuronal loss in the substantia nigra, occasionally with NFTs, (3) scarring of the cerebellar tonsils, and (4) cavum septum pellucidum. The neuropathological characterization of CTE has undergone further iterations¹³. As per the National Institute of Neurological Disorders and Stroke (NINDS)-funded study entitled, "Understanding Neurologic Injury in Traumatic Encephalopathy (UNITE)", the CTE pathognomonic lesion is defined as p-tau aggregates as neurofibrillary tangles (NFT) in neurons, with or without p-tau in astrocytes, deposited around small blood vessels, in an irregular pattern at the depths of the cortical sulci, typically involving superficial cortical layers¹⁴. The NINDS panel concluded that the pattern of p-tau in CTE is distinct from that of any other neurodegenerative disease. The molecular structure of tau filaments in CTE has also since been shown to be unique with a different characteristic conformation of the β -helix region, creating a hydrophobic cavity that is absent in tau filaments from the brains of Alzheimer's disease patients¹⁵.

McKee et al. reported β -amyloid deposition, an essential feature of AD, in 43% of CTE cases¹⁶. The number of neuritic plaques seen even in late-stage CTE cases (with or without concomitant AD-diagnostic pathology) was significantly lower than those found in pure AD controls. The pure CTE cases showed tau deposition in a prominent perivascular distribution, and an absence of β -amyloid deposition using immuno-histochemical techniques, which is a pattern of neurodegenerative changes consistent with previous characterizations of neuro-degenerative changes in CTE and a pattern distinct from that typically seen in AD¹⁴. Gardner et al. performed a systematic review of 85 athlete autopsies and found that only 20% had pure CTE, 52% appeared to have CTE plus other neuropathology, 5% had no CTE, and 24% had no observed neuropathology, leading the investigators to highlight the heterogeneity of the disease¹⁷.

McKee et al.² described CTE to have four progressive neuropathological stages. In stage 1, brains are typically of normal weight and show focal epicenters of perivascular p-tau, NFTs, neutrophil neurites, and astrocytic tangles involving the sulcal depths, especially of the superior and dorsolateral frontal cortices. Occasional degeneration p-tau immunoreactive glia and glial processes, TDP-43 neurites, and white matter reactive microglia clusters with axonal swellings are also observed. In Stage 2, brains are typically of normal weight with more frequent epicenters at the depths of the sulci and NFTs are scattered throughout superficial cortical layers as well as the locus coeruleus and substantia innominata. The lateral and third ventricles are often mildly enlarged, along with a cavum septum pellucidum and pallor of the locus coeruleus and substantia nigra. In stage 3, the brain is typically reduced in weight with mild cerebral atrophy and ventricular dilatation. Septal abnormalities are more common. There is depigmentation of the locus coeruleus and substantia nigra, as well as atrophy of the mammillary bodies, thalamus, and hypothalamus. Thinning of the corpus callosum is also typical. P-tau pathology is widespread in the broader cortical areas, and NF pathology is seen in the olfactory bulbs, amygdala, hippocampus, hypothalamus, mammillary bodies, nucleus basalis of Meynert, substantia nigra, dorsal and median raphe nuclei, locus coeruleus, and entorhinal cortex. In Stage 4, brains have a marked reduction in weight due to generalized cerebral cortical atrophy of the medial temporal lobe, thalamus, hypothalamus, and mammillary bodies. Septal abnormalities are seen in most cases. Complete depigmentation of the locus coeruleus and substantia nigra can be observed (Figure 2).

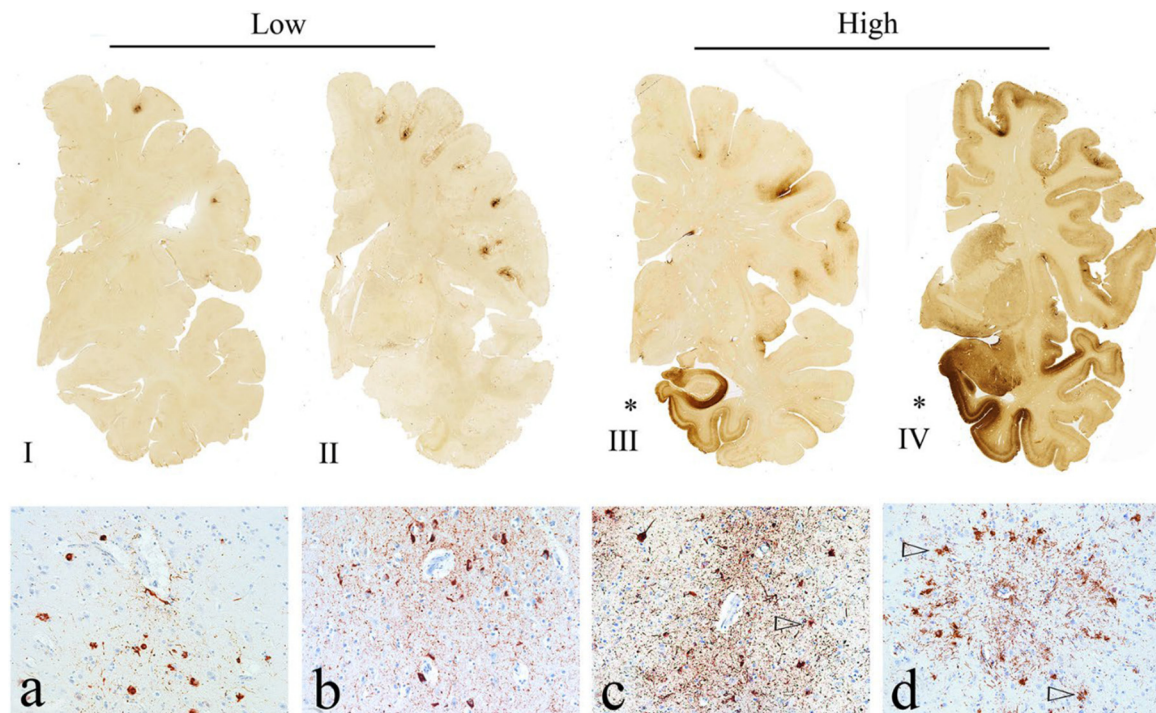


Figure 2. Top panel: Depiction McKee staging system (I-IV). McKee Stage I CTE is define by one or two isolated CTE lesions at the depths of the cortical sulci. In stage II, there are typically three or more cortical CTE lesions. In stage III CTE, there are multiple loci of CTE lesions and diffuse NFTs in the medial temporal lobe. In stage IV CTE, CTE lesions and NFTs are ubiquitously distributed throughout the cerebral cortex, diencephalon, and brainstem. Bottom panel: **a** Pathognomonic CTE lesion in stage I CTE using AT8 positive neurofibrillary tangles, dot-like and threadlike neurites surrounding a small blood vessel. **b** Characteristic CTE lesion in stage II CTE. A cluster of AT8 positive neurofibrillary tangles and dense dot-like neurites encircling several small blood vessels, **c** Defining CTE lesion in stage III CTE. A large collection of AT8 positive neurofibrillary tangles and dense dot-like neurites enclose several small blood vessels. **d** Pathognomonic CTE lesion in stage IV CTE. A large accumulation of AT8 positive neurofibrillary tangles. [Images adopted from McKee at al. *Acta Neuropathologica* 2023¹⁹⁵].

Some staging features are only found in a few cases cited as CTE, making the identification of stage-defining criteria complex. These stages arose from multiple case studies of the examined brains and are therefore based on cross-sectional rather than longitudinal data ¹⁴. It is well established that tau pathology and β -amyloid depositions can be found in adults who are healthy or have diverse health conditions. In a study by Bieniek et al., the investigators found cortical tau pathology consistent with CTE in 32% of 66 athletes with a history of contact sports compared with 0% of 198 age- matched controls in the same brain bank¹⁸. Stern et al. examined the clinical presentation of CTE in 36 patients with neuropathologically confirmed CTE ¹⁹. The results of the study suggested that the existence of two distinct clinical presentations of CTE. One group had initial changes in behavior or mood, prior to the onset of cognitive disturbances and with an earlier age onset (n =22), and the other group had initial changes in cognition and an older age of onset (n = 11). There was also an understated third group who were asymptomatic. Memory disturbances were predominant in patients in the cognitive group, who were also older, but three quarters of the behavior/mood group also had significant memory impairments. Other studies, including the one by Hampshire et al. reported abnormal functional changes on functional MRI in the activation of the dorsal frontoparietal network of retired NFL players compared with healthy controls ²⁰.

3. Potential TES Biomarkers

As CTE is largely a postmortem diagnosis, the precise diagnosis of traumatic encephalopathy syndrome remains largely elusive. The clinical diagnosis of TES would largely depend on neuroimaging, along with CSF and plasma biomarkers (see Table 1.), that would be measurable in the clinical setting. Although there is no consensus on a set of TES biomarkers, there is agreement on a set of converging neuroimaging, and so CSF/plasma markers warrant further discussions.

Table 1. TBI Plasma Biomarkers. Summary of reported TBI serum markers including GFAP (Glial Fibrillary Acidic Protein), NfL (Neurofibrillary light chain), total tau, NSE (Neuron Specific Enolase), UCHL-1 (Ubiquitin C-terminal hydrolase-1), S100B, SBDP (Spectrin Breakdown Products), MBP (Myelin Basic Protein), MAP-2 (Microtubule-Associated Protein-2), BDNF (Brain Derived Neurotrophic Factor), microRNA, and MV/E (microvesicles and exosomes).

GFAP	Clinical TBI studies have reported longitudinal elevation in GFAP levels ²⁷ . GFAP was also recently approved by the FDA as a TBI outcome clinical measure ⁴⁷ .
NfL	Clinical TBI studies have reported elevated NfL serum levels both acutely and longitudinally ²⁷ .
Tau (total)	Total tau elevation has been reported both acutely and chronically in TBI populations ²⁷ .
NSE	NSE elevated levels have reported in both mild and more severe TBI populations ^{31,32} .
UCHL-1	UCHL-1 has been shown to be robustly elevated in both mTBI and more severe TBI patients ¹³⁴ . UCHL-1 was recently FDA approved as a TBI outcome clinical measure ⁴⁷ .
S100B	S100B has been reported to be more acutely elevated in various TBI severity cases ^{48,49} .
SBDP	SBDPs are products of calpain and caspase-3 post TBI, and have been reported to be elevated in both preclinical and clinical studies ^{56,65} .
MBP	MBP is an oligodendrocyte protein and a product of proteases including calpain and reported to be elevated in severe TBI patients ^{43,64} .
MAP-2	An emerging biomarker for TBI patients ³⁹ .
BDNF	Mainly reported in the preclinical TBI studies, with potential application to clinical TBI population ⁶⁷ .
microRNA	a class of small endogenous RNA molecules, and has been reported to be elevated in biofluid (CSF, serum, or plasma) in several rodent models of TBI of various severities ⁶⁹ .
MV/E	lipid-bilayered, encapsulated particles (10–100 nm in diameter) that are released from cells into the CSF and blood during TBI ⁷³ . reported elevated MV/E released into CSF in TBI patients ⁷⁴ .
Proinflammatory cytokines (IL-6, IL-1, IL-8, IL-10, TNFα, CRP)	Proinflammatory markers, especially IL-6 and CRP have been shown to have robust diagnostic and prognostic value (ref).

3.1. Neuroimaging

Asken et al.²¹ reported data from a total of 18 structural MRI scans obtained from nine patients with TES (n = 5 with 2+ scans; first available scan: 4.1 – 1.4 years before death, range 2–6 years; last available scan: mean 2.7 – 2.6 years before death, range 0–6 years). The regions of interest (ROIs) selected included dorsal frontal, ventral frontal, temporal, parietal, occipital, thalamus, and the medial temporal subset of the overall temporal lobe. Structural MRIs obtained for each patient were

evaluated for the presence or absence of cavum septum pellucidum (CSP) by the lead investigator and verified by a second investigator. If present, the grade and length of the CSP were reported. All nine patients had a CSP (Grade 3, $n = 6$; Grade 2, $n = 3$; mean length = 15.6 ± 4.9 mm) with no clear differences between patients with High CTE (Grade 3, $n = 3$; Grade 2, $n = 1$; mean length = 15.8 ± 4.8 mm) versus without CTE. Significant medial temporal atrophy was noted on structural MRI closest to death among all nine patients irrespective of neuropathological diagnoses. The thalamus was also a common area of atrophy. Both the ventral frontal cortex (8/9 patients) and dorsal frontal cortex (7/9) had voxels with significant atrophy in most patients, although the common regions were relatively small within the larger ROIs. Smaller regions where all four patients with High CTE had significant atrophy were seen in the ventral and orbitofrontal cortex, and right posterolateral frontal cortex. Five of the nine patients underwent longitudinal MRI scans. Medial temporal and thalamic regions consistently had the lowest volumes at the initial visit and seemed to show more rapid volume decline than other ROIs.

There is insufficient evidence for the use of diffusion tensor imaging (DTI) to characterize, diagnose, and prognosticate at the individual TES patient level. However, there is a number of intriguing studies that have been reported correlating affective changes with DTI measures. With regard to white matter changes, Strain et al used DTI to examine 26 retired NFL players and found a significant association between depression symptom severity and disruption of white matter integrity²². Retired impaired NFL players also showed an increase in deep white matter lesions on T2-weighted fluid-attenuated inversion recovery when compared with matched controls but not when compared with the unimpaired retired NFL players²². In the study by Asken et al.²¹, six patients underwent antemortem DTI ($N = 3$ with High CTE; $N = 1$ with Low CTE; $N = 2$ with no CTE). All six patients had significantly diminished fractional anisotropy (FA), along the fornix irrespective of neuropathological diagnoses. Five of the six patients had significantly decreased FA in the genu of the corpus callosum (genu CC ROI median W score = -1.24) and medial temporal white matter in the areas of the uncinate fasciculus and cingulum-hippocampal bundle.

In the study by Asken et al.²¹, five patients underwent antemortem FDG-PET ($n = 2$ High CTE, $n = 1$ Low CTE, $n = 2$ no CTE). Glucose hypometabolism correlated with common areas of atrophy. Confluent areas of hypometabolism were observed in the thalamus of four of five patients. Four of five patients also showed hypometabolism in the MTL, and three of five patients had hypometabolism in the left dorsal frontal cortex.

PET imaging using tau-specific tracers have been developed with the aim of an in vivo CTE diagnosis. These tracers have been validated mainly in preclinical studies of AD and in postmortem AD cases, demonstrating increased tau ligand binding in the cortex of patients with AD compared to healthy age-matched controls²³. A growing area of interest involves the potential ability of tracers to sensitively and specifically identify p-tau aggregates that are seen in CTE versus those in other neurodegenerative diseases that involve tau. In a study by Stern et al.²⁴ involving 26 former NFL players and 31 control subjects, flortaucipir positron-emission tomography (PET) and florbetapir PET was employed to measure the deposition of tau and amyloid-beta, respectively, in the brains of former NFL players with cognitive and neuropsychiatric symptoms, and in asymptomatic men with no history of traumatic brain injury. The regional tau standardized uptake value ratio (SUVR), which is the ratio of radioactivity in a cerebral region to that in the reference cerebellum, was used to explore the associations of SUVR with symptom severity and with years of football play in the former-player group versus the control group. The inclusion criteria for the former players were male sex, age 40 to 69 years, a minimum of 2 years playing football in the NFL, a minimum of 12 years of total tackle football experience, and cognitive, behavioral, and mood symptoms reported by the participant through telephone screening. Each participant underwent flortaucipir PET, florbetapir, and T1-weighted volumetric MRI of the head. The mean flortaucipir SUVR was higher among former players than among controls in three regions of the brain: bilateral superior frontal (1.09 vs. 0.98 ; adjusted mean difference, 0.13 ; 95% confidence interval²⁵, 0.06 to 0.20 ; $P < 0.001$); bilateral medial temporal (1.23 vs. 1.12 ; adjusted mean difference, 0.13 ; 95% CI, 0.05 to 0.21 ; $P < 0.001$); and left parietal (1.12 vs. 1.01 ; adjusted mean difference, 0.12 ; 95% CI, 0.05 to 0.20 ; $P = 0.002$). All of the former NFL players in the

study reported cognitive symptoms, and more than 35% had impaired delayed-recall scores on an objective memory test.

3.2. CSF

A number of studies have proposed the use of CSF as a potential CTE biomarker. Neurofilament light (NfL) polypeptide and tau protein in the CSF have been found to be elevated immediately after boxing matches, and these elevations normalize in the following days and weeks after rest from head injury²³. A study evaluating total tau (t-tau) plasma levels reported that all former NFL players had a concentration greater than or equal to 3.56 pg/mL, indicating that t-tau elevations may be a promising biomarker for the presence of remote head injuries, occurring in patient's distant past²⁶. t-tau serum elevations were seen exclusively in former players, and levels did not correlate with cognitive testing. t-tau elevations are also seen in other neurodegenerative and cerebrovascular conditions, limiting its specificity. Hence, T-tau is likely a general marker of brain injury that occurs with a variety of disorders, including AD, frontotemporal degeneration, and stroke, but has less specificity for CTE.

3.3. Plasma

Asken et al. examined antemortem plasma GFAP, NfL, and total tau for eight of the nine patients with TES²¹. Five patients had longitudinal GFAP and NfL data, and two had longitudinal total tau data. Most patients had elevated plasma GFAP, NfL, and total tau at their initial visit compared to age-matched healthy controls. Three of five patients with longitudinal GFAP and NfL data demonstrated increasing concentrations over time, and four had increasing NfL over time.

In aging cohorts, plasma GFAP was tightly linked to AD- related α -beta 42 plaque²⁷⁻²⁹. The mechanisms underlying plasma GFAP changes in patients without AD remains to be determined, but could reflect astrocytic dysfunction and inflammation in non-AD disease pathogenesis. AD-based biomarkers such as A β -PET, CSF A β - and phosphorylated tau, or plasma phosphorylated tau in studies of patients with previous repetitive head impacts and TES may add to more specific biomarker signatures that are specific to CTE and minimize risk of misattributing biomarker changes to AD (co)pathology.

Neuron specific enolase (NSE) is also known as gamma-enolase or enolase 2 (encoded by ENO2 gene), exists as a homodimer in mature neurons and neuroendocrine cells³⁰. NSE is elevated in blood in both mTBI, as well as more severe TBI patients³¹⁻³⁶. The main challenge of using NSE in the clinical setting is the fact that it is also abundantly expressed in red blood cells, which prompted researchers to use a hemolysis correction when measuring NSE in blood³⁷. Ubiquitin C-terminal hydrolase-L1 (UCH-L1) is a protein that mainly resides in the neuronal cell body cytoplasm³⁰. UCH-L1 was first reported to be released into CSF and serum among severe TBI patients^{34,38-42}. The use of CSF UCH-L1 is a potentially robust clinical outcome predicting marker of mortality following non-penetrating TBI⁴³. UCHL-1 was also reported to be elevated in serum/plasma in mTBI, including athletes after concussion^{44,45}. Based on the results of a multi-center TBI study (ALERT-TBI), GFAP and UCHL-1 have been shown high sensitivity (0.976) and negative predictive value (0.996) for detection of traumatic intracranial injury in the acute setting⁴⁶. These robust TBI biomarker findings ultimately led to FDA approval of GFAP and UCHL-1 to aid in TBI evaluation in a clinical setting⁴⁷.

S100B is an astroglial 11 kDa calcium-binding protein. It is one of the most examined brain injury biomarkers^{48,49}. S100B has been studied in various TBI severities^{50,51}. One important confounding factor regarding the use of S100B as a TBI biomarker is that fact it can also be released from adipose tissue and cardiac/skeletal muscles, and S100B levels are also elevated in orthopedic trauma without head injuries⁵². Despite these confounding factors, S100B is actually a sensitive biomarker for predicting CT abnormality and post-concussive syndrome (PCS) development among mTBI patients⁵³⁻⁵⁵.

C-terminal breakdown products (BDPs) of axonal protein α II-spectrin (SBDP150 and SBDP145) byproduct of calpain, and SBDP120 produced by caspase-3, have been identified as potential cell death biomarkers in both preclinical models of TBI and human CSF samples^{52,56-63}. The N-terminal

spectrin fragment (SNTF) (~140 kDa) was also demonstrated to be elevated in circulation after concussion^{52,56,57,63}. One caveat to consider is that the α II-spectrin protein, although enriched in the CNS, is also expressed in other organs as well as peripheral blood mononuclear cells (PBMC)³⁰.

Myelin basic protein (MBP) is an oligodendrocyte protein and a main component of the myelin sheath that covers nerve fibers. MBP degradation as a result of activation of proteases including calpain, might be released in biofluids after TBI. MBP was found to be elevated in severe TBI in pediatric and adult populations^{43,64}.

There is a set of emerging TBI biomarkers which includes dendritic protein microtubule-associated protein-2 (MAP-2)^{65,66}, brain-derived nerve growth factor (BDNF)⁶⁷, and postsynaptic protein neurogranin⁶⁸. In addition, microRNA (miRNA), a class of small endogenous RNA molecules (19–28 nt), which regulates gene expression at the posttranscriptional level, has been reported to be elevated in biofluid (CSF, serum, or plasma) in several rodent models of TBI of various severities⁶⁹. Redell et al. reported elevations of three miRNAs (MiR-16, MiR-92a, MiR-765) in acute plasma samples after severe TBI⁷⁰. Similar studies have identified a total of 10 candidate miRNAs using acute CSF and/or serum samples from human TBI that range from mild to severe TBI^{30,71}. Another recent study showed that two miRNAs (miR-142-3p and miR-423-3p) can potentially identify mild TBI patients who are likely to develop PCS chronically⁷².

Another promising area of TBI biomarker study is the study of circulating microvesicles and exosomes (MV/E) in CSF and/or blood after TBI⁷³. Exosomes and microvesicles are lipid-bilayered, encapsulated particles (10–100 nm in diameter) that are released from cells into the CSF and blood during disease, including TBI, and often contain distinct proteins or miRNA content⁷⁴. Manek et al. reported elevated MV/E released into CSF in TBI patients containing elevated levels of several protein biomarkers (SBDPs, synaptophysin, UCH-L1, and GFAP)⁷⁵. Nekludov et al. also found that microvesicles isolated from TBI subject plasma (n = 15) contained brain-derived GFAP and aquaporin-4⁷⁶. Circulating exosomes that contain Tau have been proposed to be a better diagnostic biomarker for chronic TBI subjects at risk of developing CTE⁷⁷.

TBI induces a cascade of secondary biological phenomena, which includes production of a series of pro- and anti-inflammatory cytokines⁷⁸. In individuals with severe TBI, increased levels of (IL)-6, IL-1, IL-8, IL-10 and tumor necrosis factor alpha (TNF α), were associated with worse clinical outcomes⁷⁹. Based on a recent meta-analysis, IL-6 was shown to be a robust potential of pro-inflammatory marker in acute mild TBI patients⁸⁰. IL-6 has also been reported to have potential prognostic biomarker value of clinical outcomes post TBI⁸¹. Moreover, as one of the outcomes of the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, high-sensitivity C-Reactive Protein (hsCRP) measured within 2 weeks of TBI was found to be a prognostic biomarker of disability 6 months later⁸². Intriguingly, posttraumatic stress disorder (PTSD), a highly comorbid psychiatric illness in brain injury patients⁸³, has been shown to be a pro-inflammatory condition associated with elevation of pro-inflammatory markers, including CRP, IL-6 and TNF α ⁸⁴. Also Depression, another highly comorbid psychiatric condition with TBI⁸⁵, has been shown to be associated with low-grade inflammation, as manifested by mildly elevated CRP levels⁸⁶.

4. Treatment

Although there are no established treatments for TES, there are pharmacological and non-pharmacological treatment options for treatment of TBI/TES symptoms. The following section provides a wide scope of potential pharmacological and non-pharmacological treatment options for TBI/TES patients.

4.1. Non-Pharmacological Management

Non-pharmaceutical regimen recommendations include cognitive rehabilitation therapy, motor therapy, mood and behavior therapy including cognitive behavioral therapy, mindfulness, the Mediterranean diet, and aerobic exercise. Vestibular rehabilitative therapy is indicated for patients with inner ear injury due to repetitive TBI. Occupational-ocular therapy is recommended for those with visual disturbances⁸⁷.

4.2. Clinical Pharmacological Management

Currently, there are no FDA-approved disease-modifying regimens available for Chronic Traumatic Encephalopathy (CTE). The existing treatments are considered “off-label” and primarily focus on alleviating symptoms. In addressing memory impairment, which is a common issue in CTE, medications originally developed for Alzheimer’s disease, such as galantamine, donepezil, and rivastigmine, have been repurposed for CTE patients⁸⁷. Additionally, to tackle apathy symptoms, stimulants like methylphenidate and dopamine agonists such as carbidopa/levodopa, pramipexole, amantadine, and memantine may be employed. Amantadine has been the subject of extensive examination in moderate to severe TBI patients. A recent meta-analysis, encompassing 14 clinical trials and 6 observational studies, demonstrated the cognitive benefits of amantadine for this patient population. Notably, the improvements in cognition were more prominent in younger patients with less severe TBIs⁸⁸. Stimulants can also prove beneficial in managing attention and concentration deficits. When dealing with depression and anxiety symptoms, selective serotonin reuptake inhibitors (SSRIs) like sertraline and escitalopram can be used, but caution is advised due to the potential risk of suicidality, as suicide cases have been documented in CTE.⁸⁹ Another promising approach for addressing working memory (WM) deficits resulting from traumatic brain injury involves the use of an alpha-2-adrenergic receptor agonist known as guanfacine. Through functional MRI imaging, a study by McAllister et al. demonstrated improvements in verbal WM in 13 mild TBI patients one month after their injury. Moreover, the group treated with guanfacine exhibited increased activation in WM circuitry, particularly in the prefrontal cortex (PFC) region.⁹⁰

4.3. Clinical Use Of Nutraceutical Regimen

The elevated metabolic rate heightens the probability of reactive oxygen species (ROS) production⁹¹. Numerous preclinical studies are dedicated to exploring the use of antioxidants in the treatment of traumatic brain injuries (TBIs). Antioxidants work by effectively diminishing the potency of various oxidizing agents, including reactive oxygen species (ROS) and reactive nitrogen species (RNS).^{91,92} Antioxidants can be broadly categorized into two types: hydrophilic (water-soluble) and hydrophobic (fat-soluble). Apart from reduced glutathione (GSH), uric acid, and coenzyme Q10, the primary sources of antioxidants are derived from dietary intake. The list of antioxidant therapies employed in the treatment of traumatic brain injuries (TBI) includes ascorbic acid (vitamin C), N-acetylcysteine (NAC), flavonoids, resveratrol, alpha-tocopherol (vitamin E), coenzyme Q10, carotenoids, omega-3 fatty acids, Pycnogenol®, and phenelzine⁹¹.

4.4. Preclinical Investigational Pharmacological Intervention

Numerous extensively studied models of traumatic brain injury (TBI) exist, encompassing non-impact head acceleration, blast wave, weight drop, fluid percussion, and controlled cortical impact (CCI) models^{93,94}. A wide array of models, including those simulating mild traumatic brain injury (mTBI), accurately mirror neuropathological features such as the presence of neurofibrillary tangles, A β , phosphorylated tau, and TDP-43 deposition, alongside injury induced indicators like microgliosis, astrogliosis, endoplasmic reticulum (ER) stress, glutamate excitotoxicity, and white matter alterations. These models also capture the long-lasting, chronic cognitive deficits and mood fluctuations associated with TBI.^{94–101} Moreover, there exists several prospective treatment targets, encompassing tau acetylation, tau phosphorylation, and the realms of neuroinflammation and immunotherapy.

4.5. Targeting Tau Acetylation

P-tau accumulation results from tau phosphorylation, preceded by ac-tau post-translational acetylation, which is likely a result of neuroinflammation, endoplasmic reticulum, and oxidative stress^{87,102,103}. Studies investigating the treatment of tauopathies have largely targeted this pathway. For example, salsalate reduced inflammation, promoted neuroprotection and neurogenesis through gene upregulation. It also prevented hippocampal atrophy, and resulted in functional reversal of

acetylation in mTBI rodent models by reducing p300 lysine acetyltransferase, inhibiting tau acetylation on lysine 174, and inhibiting microgliosis^{104,105}. Methylene blue, which modulates K280/K281 acetylation activity, was reported to increase neuroprotection, diminish behavioral deficits and mood changes, and minimized neuronal degeneration, neuroinflammation, lesion volume, microgliosis, and mitochondrial dysfunction in TBI rodent models^{106–108}. Histone deacetylase 6 (HDAC) and sirtuins (SIRT1 and SIRT2) increased tau deacetylation, presenting another potential treatment methodology that targets the same pathway mechanism but in a different manner¹⁰⁹.

4.6. Targeting Tau Phosphorylation

Kinase inhibition has also been effectively explored in preclinical models. Glycogen synthase 3 beta (GSK-3 β) which is activated by p-tau to cause further tau phosphorylation, promoted amyloid- β related cell death, and downregulated antioxidant defenses like nuclear factor E2-related factor 2 (Nrf2)^{87,110–112}. Dimethyl fumarate (DMF) modulated GSK-3 β activity, induced the Nrf2 transcriptional signature, and modulated astrogliosis and microgliosis in tauopathy mouse models¹¹³. The blocking of GSK magnesium binding by lithium led to GSK phosphorylation. It also blocked receptor tyrosine kinase activity, diminished neurodegeneration, maintained the integrity of the blood-brain barrier, improved cognitive outcomes, and diminished lesion sizes in a TBI preclinical mouse model^{114–120}. Lithium may treat many CTE features like mood, impulsivity, suicidal ideation, and depression. Valproic acid, alone or administered with lithium, results in neuroprotection and improved functional outcomes. The GSK3 inhibitor L803-mts prevented TBI-induced depression in mTBI weight-drop rodent models¹¹⁵. Several studies demonstrated that cyclin dependent kinase (CDK) inhibitors (roscovitine and its derivative CR-8) diminished neuroinflammation and neurodegeneration while improving functional outcomes in TBI rat models¹²¹. A prior study has shown that the combined use of lithium and roscovitine led to more prominent reductions in cortical and blood p-tau when used in combination rather than when used alone in a mouse model of repetitive mild TBI¹⁰¹. Using a preclinical CTE model based on combined repetitive mild TBI and chronic stress, Tang and Fesharaki-Zadeh et al., examined the long-term pharmacological use of Fyn Kinase inhibition, AZD0530. Post-injury Fyn inhibition led to a reduction of focal phospho-tau accumulation, as well as neurobehavioral rescue as measured by rescuing object recognition and improving spatial memory function (Figure 3)⁹⁴.

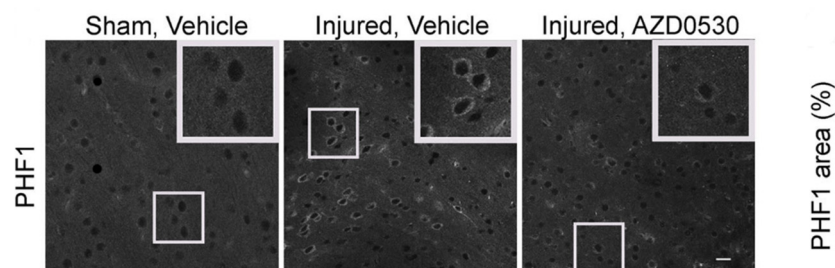


Figure 3. Representative images using immunofluorescent staining for PHF1 of coronal cerebral cortex sections within 0.5–1 mm medial to the site of injury in 7.5-month-old control mice from SV (Sham Vehicle treated), IV (Injured Vehicle treated), and IA (Injured AZD0530 treated) groups. [Images adopted from Tang et al. *Acta Neuropathologica Communications* 2020⁹⁴].

4.7. Targeting Inflammation

Damage and cellular demise lead to the extracellular release of various ions, molecules, and proteins collectively known as damage-associated molecular patterns (DAMPs).^{122,123} These DAMPs encompass ATP and K⁺, double-stranded DNA, and the high mobility group 1 (NMG1) chromatin protein. ATP binds and activates P2 $\times$ 7 receptors, while elevated K⁺ stimulates pannexin receptors¹²⁴. DAMPs bind extracellular receptors that activate intracellular inflammasomes¹²⁴. Activated inflammasomes in neurons and astrocytes convert pro-IL-1 β and pro-IL-18 into its biologically active forms¹²⁵. Extracellular IL-1 β and IL-18 levels increase acutely post injury and are the main inducers

of microglia and other early inflammatory processes¹²⁴. $\text{TNF}\alpha$, IL-6, IL-12 and interferon γ are additionally released in acute phase of injury¹²⁴. Neurovascular changes, infiltration of peripheral inflammatory cells and activation of resident microglia and astrocytes leads to a more global release of cytokines, chemokines, and bioactive lipids^{126,127}. The alteration of microglia activation is a key event in switching from inflammation with early and largely deleterious effects to a later phase of tissue repair and remodeling¹²⁶. Microglia can differentiate into either pro-inflammatory M1 or an anti-inflammatory M2 phenotypes¹²⁸. M1 microglia intensify inflammation, bolster the presence of pro-inflammatory cells, and facilitate the clearance of apoptotic cells. They secrete pro-inflammatory cytokines, including IL-1 β , $\text{TNF}\alpha$, and IL-6, along with chemokines that attract more inflammatory cells to the site of injury. Moreover, M1 microglia amplify oxidative stress through elevated expression of NADPH oxidase and iNOS.¹²⁹ All subtypes of M2 microglia exhibit anti-inflammatory characteristics^{128,130}. M2a microglia play a pivotal role in mitigating inflammation, promoting cell proliferation and migration, and facilitating tissue repair. M2b microglia express toll-like receptors and exhibit high levels of arginase-1, IL-1, $\text{TNF}\alpha$, IL-6, and CD86. The exact function of M2b microglia is not fully elucidated, but they seem to possess a dual role involving both pro- and anti-inflammatory activities. M2c microglia also contribute to anti-inflammatory processes, distinct from M2a microglia, by expressing elevated levels of TGF β , CD206, CD163, and sphingosine kinase 1.¹³⁰ The precise identification of the inflammatory mediators essential for achieving optimal therapeutic effects remains an ongoing challenge¹³¹.

Previous investigations have aimed at addressing the intricate inflammatory cascade and metabolic changes in preclinical models of CTE. A recent study specifically centered on the potential application of the pyrimidine derivative OCH, which is believed to safeguard mitochondrial function and maintain adequate ATP synthesis following traumatic brain injury (TBI).¹³² OCH demonstrated enhancements in ATP production, respiratory efficiency, and cerebral blood flow, coupled with reductions in glycolysis activity, CTE biomarker levels, and β -amyloid concentrations. Furthermore, OCH treatment effectively preserved sensorimotor function.¹³² The use of salubrinal (SAL), a stress modulator, significantly diminished ER stress, oxidative stress, pro-inflammatory cytokines, and inducible nitric oxide synthase. SAL treatment also reduced impulsive-like behavior in rodent models of repetitive TBI.¹³³ Calpain-2 has been implicated in the progression of neurodegeneration subsequent to TBI. The application of a selective calpain-2 inhibitor, known as C2I, resulted in a significant reduction in calpain-2 activation. This intervention effectively halted the elevation of tau phosphorylation and TDP-43 alterations, curbed astrogliosis and microgliosis, and successfully mitigated cognitive impairment in a preclinical model of repeated mild traumatic brain injury.¹³⁴ Inhibiting monoacylglycerol lipase (MAGL), responsible for the metabolism of 2-arachidonoylglycerol (2-AG), yielded significant reductions in neurodegeneration, tau phosphorylation, TDP-43 aggregation, astrogliosis, and proinflammatory cytokines. This intervention also resulted in improved cognitive outcomes in a rodent model of repetitive mild TBI. Additionally, the application of 2-AG enhanced blood-brain barrier integrity and reduced the expression of inflammatory cytokines when utilized in a preclinical CHI rodent model.¹³⁵

Glucocorticoids exert a broad anti-inflammatory effect by inhibiting the synthesis of interleukins and bioactive lipids. They also suppress cell-mediated immunity, reduce leukocyte count and activity.¹³⁶ Despite several preclinical studies, none have investigated whether the anti-inflammatory properties of dexamethasone translate into improved brain function¹²³. Clinical trials have yielded limited success, likely due to a narrow therapeutic window¹³⁷. A significant phase III trial, known as CRASH (corticosteroid randomization after significant head injury), included 10,008 adults with TBI and a Glasgow Coma Score (GCS) ≤ 14 .¹³⁷ Within 8 hours of the injury, these patients received a 48-hour infusion of methylprednisolone or a placebo. Intriguingly, the methylprednisolone group exhibited a higher risk of mortality compared to the placebo group, irrespective of the injury severity, thus diminishing the potential clinical efficacy of this regimen.

Non-steroidal anti-inflammatory drugs (NSAIDs) represent a class of medications known for their potent analgesic, antipyretic, and anti-inflammatory properties achieved through the inhibition of COX-1 and COX-2.¹³⁸ COX-2 selective drugs like carprofen, celecoxib, meloxicam, nimesulide,

and rofecoxib have undergone testing in various preclinical TBI models¹³⁹. Despite their anti-inflammatory potential, these agents have not proven sufficiently effective in targeting COX-1 or COX-2, making them less promising as therapeutic options for TBI treatment¹²³. TNF α is a pro-inflammatory cytokine that is rapidly induced by traumatic injury¹²⁶. Inhibition of TNF α via the use of HU-211, a synthetic cannabinoid, produced long-term improvements in Morris water maze, beam walking and balancing. When administered within two hours post-injury, it led to reduced edema and improved blood-brain barrier integrity¹³⁹. Another potent TNF α antagonist, decreased IL-1 β and IL-6 at 3 days post-injury and decreased TNF α at both 3 and 7 days post-injury¹⁴⁰. Similar to TNF α , IL-1 β is an acute proinflammatory cytokine whose expression increases rapidly after injury¹⁴¹. Mice engineered to overexpress IL-1ra, a decoy receptor for IL-1 β , had less edema one-day post-injury and improved neurological scores between 1 and 14 days post-injury¹⁴². Administration of anakinra, a recombinant human IL-1 receptor antagonist, two hours after experimental TBI had little effect on lesion volume, rotarod for motor assessment, or Morris water maze for spatial memory¹⁴³. In a phase II randomized control clinical trial, administering anakinra within 24 h of injury modified the neuroinflammatory response, but given the small study size, it was not determined whether anakinra had a therapeutic effect¹⁴⁴.

Phosphodiesterase inhibitors diminish the breakdown of the second messenger cyclic AMP to 5'AMP¹²³. Rolipram, an inhibitor of phosphodiesterase IV, modified histology and function when dosed 30 min prior to injury¹⁴⁵. Dosing Rolipram 30 min post injury produced a similar reduction of IL-1 β and TNF α levels 3 h after injury yet lesion size was increase over vehicle controls¹⁴⁶.

Minocycline is a lipophilic tetracycline-based antibiotic that can cross the BBB, with anti-inflammatory action at higher concentrations¹⁴⁷. Multiple prior studies have demonstrated the anti-inflammatory effects of minocycline^{148,149}. Dosing of minocycline between 5 min and 1 h after injury improved performance on a variety of behavioral tasks including novel object recognition, elevated plus maze, Morris water maze and active place avoidance^{148,150}. Lowered production of IL-1 β likely underlies the inhibitory action of minocycline on microglia¹⁵¹. The combination of minocycline and N-acetylcysteine (NAC), synergistically improved memory in Active Place Avoidance (APA) task, a complex spatial memory task¹⁵⁰.

Progesterone, a gonadal hormone, exhibits multiple anti-inflammatory actions¹⁵². When administered 30 minutes post injury, progesterone initially increased IL-1 β levels at 6 h, with subsequent lowering levels at 24 h. IL-6 was inhibited at both 6 and 24 h post-injury. Progesterone decreased TNF α at 6 h post-injury and increased TGF β levels 24 h after injury¹⁵³. The PROtect phase II trial included seventy-seven patients in a group that received progesterone and 23 patients in a group that received placebo within 11 h of injury¹⁵⁴. Patients began progesterone treatment 6.3 ± 2.1 h post injury. Patients receiving progesterone had a lower 30-day mortality rate than control group. Patients with moderate traumatic brain injury had better clinical outcomes on the Glasgow Outcome Scale-Extended test and Disability Rating Scale. A large, multi-center Phase III PROtect III trial, examined whether progesterone produced a more favorable functional recovery as compared to placebo using the Extended-Glasgow Outcome Score 6 months post injury¹⁵⁵. The study was terminated after no significant effect was observed in 882 patients. A second large scale trial (SYNAPSE) examined progesterone given to 569 study subjects when dosed to severe TBI patients (Glasgow Coma Score < 8)¹⁵⁶. Progesterone did not differ from control in any of the study outcomes based on Glasgow Outcome Score at 3 months, reduced mortality at 1 and 6 months, and the Extended-Glasgow Outcome Score at 6 months.

Erythropoietin controls proliferation of erythrocyte precursors in bone marrow, and based on a number of preclinical models of TBI and stroke, erythropoietin has demonstrated anti-apoptotic, anti-oxidative, angiogenic, and neurotrophic activities¹⁵⁷. When dosed 5 minutes after injury, erythropoietin effectively reduced IL-1 β , IL-6 and CXCL2¹⁵⁸. One hour dosing of erythropoietin prevented increased IL-1 β and microglia later after injury in a model that combined weight drop and hypoxia one-hour dosing of erythropoietin prevented increased IL-1 β and microglia later after injury¹⁵⁹. Erythropoietin was compared with high or low hemoglobin transfusion in 200 patients with a closed head injury having a Glasgow Coma Score > 3 ¹⁶⁰. Transfusion was initiated within 6 h after

injury. Patients were transfused to maintain a hemoglobin threshold of 7 or 10 g/dl and either received erythropoietin or placebo. In a separate observational study, erythropoietin therapy was administered within the first 2 weeks post injury, with patients on erythropoietin treatment having significantly longer stays in the intensive care unit, in turn potentially suggestive of a longer survival¹⁶¹. The evidence for the use of erythropoietin has not reached the threshold for its use in a phase III trial¹²³.

Anakinra, a recombinant human IL-1 receptor antagonist (IL-1ra), was studied in a phase II randomized control clinical trial, assessing neuroinflammatory modulation using anakinra following TBI¹⁴⁴. This trial involved the study of twenty TBI patients with a Glasgow Coma Score of ≤ 8 , who were recruited within the first 24 hours after the injury. Using microdialysis probes within the brain parenchyma, various cytokines including IL-1ra were examined. CCL22 levels were reported to be significantly lowered in the anakinra group. The study was too small to establish anakinra as an effective clinical regimen but provided an intriguing approach for the use of extracellular fluid as a probe as opposed to baseline serum or CSF markers.

A limited number of previous studies have explored the use of statins for TBI, with two notable large observational trials. In one of these trials, conducted by Schneider et al., 523 patients with moderate to severe TBI (Abbreviated Injury Score of ≥ 3) were observed¹⁵². Among the patients, 22% were regular users of statins¹⁶². The statin users were found to have a lower risk of in-hospital death. At one year assessment of Extended Glasgow Outcome Scale of the 264 remaining patients, statin users had a small, but significantly higher likelihood of more optimal recovery, but the net therapeutic effect of statins was not measurable once controlled for cardiovascular comorbidities in statin users.

4.8. Immunotherapy

Immunotherapy employing monoclonal antibodies has also been a subject of investigation in preclinical studies focused on tauopathies⁸⁷. A recent study demonstrated that the delivery of an adeno-associated virus (AAV) vector coding for an anti-p tau antibody reduced CNS p tau levels in rodent models of repeated traumatic brain injury¹⁶³. Furthermore, in an in-vitro study, several tau antibodies demonstrated their efficacy in preventing neuronal tau uptake. Specifically, the antibody 6C5 successfully thwarted interneuronal propagation and the progression of tau aggregation after cellular uptake¹⁶⁴.

Specific antibodies targeting the pathogenic cis-P-tau post TBI have been reported to lead to improved structural and functional outcomes¹⁶⁵⁻¹⁶⁷. Removal of microglia using PLX5622, a colony-stimulating factor 1 receptor (CSF-1R), was reported to have little effect on the outcome of TBI, but induction of turnover of these cells via either pharmacologic or genetic approaches can result in a neuroprotective microglial phenotype and profound recovery post TBI. The beneficial properties of these repopulating microglia is critically dependent on interleukin-6 (IL-6) trans-signaling via the soluble IL-6 receptor (IL-6R) and robustly promote adult neurogenesis¹⁶⁸.

4.9. Potential dietary targets

The consumption of a Western diet (WD) and the associated obesity have been consistently linked to systemic inflammatory responses, cognitive decline, and worsened outcomes following brain injuries¹⁶⁹⁻¹⁷¹. WD-induced secretion of interleukins such as IL-1 b and IL-6 can disrupt neural circuits involved in cognition and memory¹⁷². In a preclinical study focused on the secondary injury outcomes resulting from a closed head injury (mTBI), obese C57 BL/6 mice fed a WD were compared to lean mice. At a chronic time point (30 days), the obese mice displayed significantly increased microglial activation and a chronic state of inflammation¹⁷³.

Ketogenic diet (KD) is a fat-rich diet low in proteins and carbohydrates, with low obesogenic, and has been demonstrated to be neuroprotective^{169,174,175}. Unlike WD, the KD diet can reduce neuronal inflammation¹⁷⁶, rescue behavioral patterns of depression in animal models¹⁷⁷, diminish cognitive defects¹⁷⁸, and modulate neuronal injury¹⁷⁹. In addition, an alternative Mediterranean diet (MD) consumption has also been associated with reduced risk of dementia and better memory and

language performance¹⁸⁰. Preclinical studies have reported that antioxidants and flavonoids from fruits and vegetables in these diets suppress neuro-inflammation by reducing oxidative stress and apoptosis via inhibition of NF-KB-dependent inflammatory signaling¹⁸¹.

5. Future Directions

Chronic traumatic encephalopathy (CTE) and traumatic encephalopathy syndrome (TES) have gained special attention in the public discourse. The diagnosis of CTE remains predominantly pathological, and in turn making the diagnosis of TES and emerging CTE pathological diagnosis challenging. As TES is a relatively novel clinical diagnostic classification, the exact prevalence of TES amongst athletes, combat veterans and civilians, remains largely unknown. A recent study encompassed 176 participants, consisting of 110 boxers and 66 mixed martial artists (MMA), who were all included in the analysis. Among them, 72 individuals (41% of the total) were categorized as having traumatic encephalopathy syndrome (TES), with the likelihood of TES increasing as age advanced. TES-positive (TES+) participants were more likely to be boxers, initiated their fighting careers at a younger age, engaged in more professional fights, and experienced more frequent knockouts¹⁸².

There are a number of diagnostic challenges, which include limited research pertaining to diagnostic validity¹⁸¹. There are also limitations pertaining to absence of universally agreed upon biomarkers³⁰. Despite proposed neuroimaging correlates for TBI and CTE, their diagnostic and prognostic utility remain elusive. Diagnostic challenges include small sample size, inherent heterogeneity of TBI/CTE among injured individuals, as well as the widely varying interval between injury and clinical assessment⁸⁷. The majority of the completed studies lack female study participants, a significant limitation and hinders clinical applicability. Given the tauopathy nature of CTE/TES, a wider use of tau markers, including tau PET ligands like flortaucapir is needed¹⁸³. Identification of sensitive and specific CTE/TES biomarkers would facilitate early diagnosis, monitoring of disease progression, as well as assessing disease prognosis. Access to validated biomarkers would also provide the necessary basis to study the natural progression of the disease in a more systematic way.

Currently, there are no FDA approved drugs for CTE/TES which would offer a disease modifying effect. Although a number of preclinical studies have proposed potential therapeutic effects for CTE⁹⁴, there is an urgent need for large scale clinical trials. Moreover, there are a number of proposed preclinical models of CTE^{94,99,184–186}, but there is no agreement on a specific animal model of CTE. The lissencephalic nature of rodent cortex also adds a layer of complexity in its application to clinical studies. Moreover, the central role of neuroinflammation is increasingly more recognized in TBI^{87,187}. Development of disease specific immunomodulating agents, including humanized monoclonal antibodies is, quite possibly, in the CTE/TES treatment horizon¹⁸⁸.

Given the lack of current treatment options, the most viable CTE/TES treatment option is prevention and safe practices. There is a great need for continuing optimization of protective sports gear, vigilant enforcement of sports contact rules and protocols, and raising public awareness^{189,190}.

One area poised for significant future advancements is development of highly sensitive and specific assays for traumatic brain injury (TBI) in serum and cerebrospinal fluid (CSF). Despite numerous studies, there is currently a lack of consensus regarding proposed biomarkers for TBI. The recent FDA approval of GFAP and UCHL-1 for acute assessment of TBI in the ED setting and examining the necessity of CT neuroimaging, is a major step forward^{46,47}. Research on other TBI biomarkers has produced mixed results. For example, two prior studies found no correlation between serum S100B concentration and clinical outcomes, as measured by tools such as the Glasgow Outcome Scale (GOS), Glasgow Outcome Scale-Extended (GOS-E), or imaging studies^{191,192}. Similarly, another study found that GFAP was not an effective clinical predictive marker based on GOS-E and functional timeline¹⁹³, while an earlier study demonstrated that serum cleaved tau (c-tau) was also not a reliable predictor after mild TBI¹⁹⁴.

The research and clinical management of chronic traumatic encephalopathy (CTE) and traumatic encephalopathy syndrome (TES) are rapidly evolving areas, as our current understanding of their neuropathological mechanisms continues to expand¹¹. Advancements in ultra-sensitive biofluid

assays would be crucial for earlier and more accurate clinical detection of CTE/TES, as well as the potential for more effective treatments. In addition, the development and refinement of disease-specific markers such as tau PET ligands would further expand the much-needed arsenal for timely and effective management of this complex disease, both in research and clinical settings.

Table 2. TBI pharmacological treatments reported in preclinical and clinical studies. An overview of the reported TBI pharmacological regimen examined in preclinical and clinical studies. A number of these regimen, including cholinesterase inhibitors, NMDA receptor antagonists, SSRIs, guanfacine, NSAIDs, as well as glucocorticoids and progesterone are cross-purposed medications that have been utilized in treatment of TBI clinical studies. Tau phosphorylation, tau acetylation and immunotherapy regimen have largely been examined in the preclinical TBI setting.

Cholinesterase Inhibitors	Cholinesterase inhibitors including galantamine, donepezil, and rivastigmine, have been repurposed for TBI patients ⁸⁷ .
NMDA receptor antagonists	NMDA receptor antagonist, amantadine, has been shown to improve cognition in moderate to severe TBI patients ⁸⁸ .
SSRIs	Selective serotonin reuptake inhibitors (SSRIs) like sertraline and escitalopram have been utilized to manage behavioral symptoms in TBI patients ⁸⁹ .
Guanfacine	Guanfacine has been reported to improve working memory deficits in mild TBI patients ⁹⁰ .
Nutraceuticals	A number of nutraceuticals have been utilized in treatment of TBI preclinical and clinical studies, including N-acetylcysteine (NAC), flavonoids, resveratrol, alpha-tocopherol (vitamin E), coenzyme Q10 ⁹¹ .
NSAIDs	COX-2 selective drugs like carprofen, celecoxib, meloxicam, nimesulide, and rofecoxib have undergone testing in various preclinical TBI models, with no significant degree of established efficacy ¹²³ .
Glucocorticoids	Despite several promising preclinical studies, clinical trials have resulted in limited success, likely due to a narrow therapeutic window ¹³⁷ .
Phosphodiesterase Inhibitors	Phosphodiesterase inhibitors have been utilized mostly in preclinical studies, and have not systematically studied in clinical trial setting ¹⁴⁶ .
Minocycline	In prior preclinical studies, minocycline given between 5 min and 1 h after injury improved performance on a variety of neurobehavioral ¹⁵⁰ .
Progesterone	A large, multi-center Phase III PROtect III trial, as well as a second larger scale trial (SYNAPSE) examined progesterone did not establish clinical efficacy ¹⁵⁶ .
Erythropoietin	Despite preclinical studies success, the evidence for the use of erythropoietin has not reached the threshold for its use in a phase III trial ¹²³ .
Anakinra	A small phase II randomized controlled clinical trial reported anti-inflammatory benefits in Anakinra treated group, but the study size was too small to establish efficacy, but provided an intriguing potential future approach ¹⁴⁴ .
Tau phosphorylation targets	The studies focusing on tau-phosphorylation targets have been mostly preclinical, with possible future clinical applications ⁹⁴ .
Tau acetylation targets	Tau acetylation inhibitors including salsalate, as well as methylene blue, as well as histone deacetylase 6 and sirtuins have largely been examined in the preclinical setting ¹⁰⁹ .
Immunotherapy	Specific antibodies targeting the pathogenic cis-P-tau post TBI have been reported to lead to improved structural and functional outcomes ¹⁶⁵ , but yet to be examined in larger clinical trial setting.

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