International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

A Review of Advances in Multimodal Treatment Strategies for Chronic Disorders of Consciousness Following Severe Traumatic Brain Injury

Shuyan Liu[1], Xueqing Li[2], Shi Jiang[1], Dan Liu[1], Jinghua Wang[1]

[1]Department of Orthopedics, Shenzhen Children's Hospital, Shenzhen, Guangdong, People's Republic of China; [2]Department of Nursing, Shenzhen Children's Hospital, Shenzhen, Guangdong, People's Republic of China

Correspondence: Dan Liu, Email hmd1974@163.com; Jinghua Wang, Email 1124436951@qq.com

---

Background: Chronic disorders of consciousness (cDoC) resulting from severe traumatic brain injury (sTBI) are associated with significant challenges in treatment and recovery. This review explores multimodal interventions aimed at improving patient outcomes.
Methods: A systematic review was conducted on peer-reviewed studies from PubMed and Google Scholar published between 2000 and 2023. The review included clinical trials, observational studies, and case series that assessed interventions for improving consciousness and cognitive function in patients with cDoC following sTBI. Interventions considered included pharmacological treatments, non-invasive neuromodulation, rehabilitation therapies, and traditional medicine approaches.
Results: The review identifies several promising interventions. Hyperbaric oxygen therapy (HBOT), when combined with physical rehabilitation and non-invasive brain stimulation techniques like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), has shown positive effects on consciousness and cognitive recovery. Non-invasive neuromodulation techniques have been linked to improvements in cortical activity and consciousness, with taVNS emerging as a novel approach. Additionally, traditional Chinese medicine, particularly herbal therapies, has demonstrated complementary benefits when integrated with modern rehabilitation methods. Personalized treatment strategies based on clinical characteristics, biomarkers, and genetic data were found to enhance recovery. Notably, integrating these modalities into personalized care protocols has shown enhanced efficacy, suggesting that individualized approaches are critical for improving outcomes.
Conclusion: Multimodal therapies show promise in enhancing recovery in cDoC patients after sTBI, but further research is needed to optimize treatment protocols and standardize clinical practices. The integration of traditional and modern therapies represents a potentially effective strategy for improving patient outcomes.

Keywords: severe traumatic brain injury, chronic disorders of consciousness, multimodal treatment, hyperbaric oxygen therapy, neurostimulation, rehabilitation training

---

Introduction

Severe traumatic brain injury (sTBI) represents a significant global health challenge and is one of the leading causes of long-term disability and death.[1,2] It frequently arises from high-energy events such as traffic accidents, falls, assaults, and sports-related impacts, often resulting in chronic disorders of consciousness (cDoC). cDoC is characterized by an impaired state of consciousness persisting for more than 28 days and includes conditions such as coma, vegetative state, and minimally conscious state. Epidemiologically, the global incidence of sTBI is substantial, with estimates suggesting that sTBI accounts for 5% to 9% of all traumatic brain injuries, though regional variability exists.[3] In developed nations, the incidence ranges from 20 to 25 per 100,000 population annually, while in developing regions, the rate may reach as high as 30 to 40 per 100,000. Additionally, studies highlight the substantial proportion of sTBI patients who develop cDoC. For example, a meta-analysis by Nguyen et al[4] reported that 10–20% of individuals with sTBI

Received: 7 November 2024
Accepted: 30 January 2025
Published: 14 February 2025

progress to cDoC, imposing significant long-term healthcare demands. The economic burden associated with sTBI is considerable, spanning direct medical expenses and indirect costs, such as loss of productivity. In the United States, Marino et al[5] estimated the lifetime cost per sTBI patient at approximately $76.5 billion. In Europe, Olesen et al[6] reported that the annual cost of traumatic brain injury, including severe cases, reached €33 billion in 2010. These financial impacts underscore the need for effective interventions to reduce both the human and economic toll of sTBI.

Despite advances in acute care, which have enhanced survival rates, the clinical management of cDoC remains highly challenging. Recovery of consciousness is often slow and incomplete. A systematic review by Giacino et al[7] found that while 38% of patients with cDoC exhibited signs of consciousness recovery within two years, many remained in states of severe impairment, emphasizing the ongoing need for therapeutic innovations. Current treatment options for cDoC are limited, and there is no universally effective approach.[8,9] In recent years, there has been increasing interest in multimodal therapeutic strategies to enhance recovery in cDoC patients.[10] These approaches integrate several treatment modalities, including hyperbaric oxygen therapy, physical and occupational therapy, and neurostimulation techniques, among others. Meta-analyses, such as the one by Kondziella et al,[11] suggest that multimodal treatments may yield superior outcomes compared to single therapies. Their pooled analysis revealed a significantly higher likelihood of consciousness improvement with multimodal approaches.

In parallel with these advancements, the field of neuroscience has witnessed a shift toward personalized treatment strategies tailored to individual patient profiles. Emerging research highlights the potential of biomarker- and genetic-based interventions to optimize recovery outcomes. For instance, a prospective cohort study by Schnakers et al[12,13] demonstrated a 25% increase in recovery rates with personalized treatment plans, compared to standard care protocols, reflecting the growing importance of precision medicine in the management of cDoC. Similarly, Haddas et al[14] showed that neurostimulation therapies tailored to the individual significantly enhanced consciousness recovery in patients with vegetative and minimally conscious states. Wilde et al[15] also highlighted the positive effects of personalized rehabilitation and the critical role of biomarkers in guiding treatment decisions. Precision medicine allows treatment strategies for sTBI patients to be adapted based on specific trauma characteristics and neurophysiological states, improving rehabilitation outcomes and reducing complications. In both sTBI and cDoC, personalized treatment offers better results, lowers healthcare costs, and improves patients' quality of life, representing a shift toward more individualized, precise care.

Given the complexity of sTBI and cDoC and the evolving landscape of therapeutic options, this review aims to provide an in-depth examination of the current state of multimodal treatment strategies for chronic disorders of consciousness following severe traumatic brain injury. By synthesizing the latest research and considering practical applications, we seek to highlight promising avenues for future clinical practice and research, with the ultimate goal of improving patient outcomes in this challenging and underserved population.

Methods

Types of Studies

We focus on studies that evaluate various rehabilitation interventions for patients with cDoC following sTBI, including clinical trials, observational studies, and case series published in peer-reviewed journals. Only studies that assess the effects of specific interventions aimed at improving consciousness, cognitive function, and quality of life in cDoC patients after sTBI were considered. The literature was screened involving all age populations, specifically those diagnosed with cDoC, including vegetative state and minimally conscious state. Only studies that included patients with stable or improving conditions were included, as these patients are more likely to benefit from rehabilitation interventions. Studies focusing on non-traumatic causes of cDoC were excluded.

Types of Interventions

The interventions can be classified into several categories: pharmacological treatments, non-invasive neuromodulation techniques, surgical interventions, rehabilitation therapies, and traditional medicine.[16,17] Pharmacological treatments, including neurotrophic factors, cholinergic agents, and dopamine agonists, were explored for their potential in promoting neurorestoration and enhancing brain function.[18] Non-invasive neuromodulation techniques, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcutaneous auricular vagus nerve stimulation (taVNS), were examined for their effects on cortical activity and potential to improve consciousness levels.[19] Surgical treatments, particularly spinal cord stimulation (SCS), were also included, as they aim to enhance brain function through direct neural stimulation.[20] In addition to these interventions, rehabilitation therapies focusing on respiratory function and swallowing, as well as traditional medicine approaches such as Chinese herbal medicine, were evaluated for their potential benefits in improving overall recovery.

Data Extraction and Search

Data was extracted from the selected studies through a systematic review of the available literature.[21] The focus was on summarizing the findings from the studies without conducting direct statistical analysis. Key results were reported in terms of qualitative outcomes, such as improvements in consciousness levels, cognitive function, and other relevant clinical measures. Notably, given the variability in study designs and interventions, we focused on synthesizing the qualitative findings to provide an overview of the effectiveness of different rehabilitation strategies.

The literature screening process was guided by a set of defined criteria to ensure the relevance and rigor of the included studies. 1) Clinical diagnosis and disease characteristics were key factors in selecting studies, focusing on patients with sTBI and cDoC. Emphasis was placed on studies with detailed diagnostic criteria, supporting neuroimaging, and clinical evidence that clearly identified the severity, location of injury, disease progression, and any comorbidities. 2) The type of therapeutic intervention was another essential criterion. We prioritized studies investigating treatments such as hyperbaric oxygen therapy (HBOT), neuroplasticity-based therapies, and early rehabilitation interventions. Only studies that provided clear descriptions of the intervention protocols—such as duration, frequency, and modality—were included, ensuring that the effectiveness of these therapies could be consistently assessed. 3) Study design and quality were also critical. Only peer-reviewed articles with high methodological standards were selected, including randomized controlled trials (RCTs), clinical trials, systematic reviews, and relevant clinical guidelines. These studies were chosen for their scientific rigor and ability to provide reliable evidence on the outcomes of interventions. 4) Our search covered publications from 2000 to 2023, ensuring that the selected studies were both recent and relevant. Studies from a range of geographical locations were also included to capture potential regional variations in treatment approaches and outcomes. 5) Only studies published in English and available in full text were considered. Literature was retrieved from key databases, including Google Scholar, PubMed, and ScienceDirect, using search terms like “traumatic brain injury”, “disorders of consciousness”, “hyperbaric oxygen therapy”, “neuroplasticity”, and “early rehabilitation”.

Data from the selected studies were then synthesized narratively, summarizing key findings and drawing conclusions to inform further research and clinical practice in the field of sTBI and cDoC management. Details shown in Table S1.

Results

Hyperbaric Oxygen Therapy (HBOT) for cDoC Patients

Hyperbaric oxygen therapy (HBOT) is a non-invasive medical treatment in which patients breathe 100% oxygen in a pressurized environment, typically set at 1.5 to 3 times the normal atmospheric pressure[22,23] (Figure 1 and Table S1). The elevated pressure increases the amount of oxygen dissolved in the blood, which in turn improves oxygen delivery to hypoxic tissues. This enhanced oxygenation boosts tissue oxygen partial pressure, augments oxygen diffusion, and supports cellular recovery in ischemic areas. HBOT has been widely utilized in the treatment of various conditions, including sTBI, non-healing wounds, carbon monoxide poisoning, and decompression sickness.[23–25] Each HBOT session typically lasts 60 to 90 minutes, with patients receiving intermittent breaks to breathe ambient air, reducing potential oxygen toxicity. The standard treatment regimen involves one session per day, for a total of 10 sessions, followed by a 3-day rest period before beginning a second cycle. This 10-day cycle is repeated, resulting in two treatment courses in most therapeutic protocols.[26,27] However, the specific pressure level, duration, and frequency of treatments can be adjusted based on the severity of the condition, patient response, and comorbidities.

In the context of sTBI, HBOT has demonstrated several neuroprotective mechanisms. It enhances cerebral oxygenation, which facilitates the metabolic recovery of injured neurons. Studies have shown that HBOT improves mitochondrial

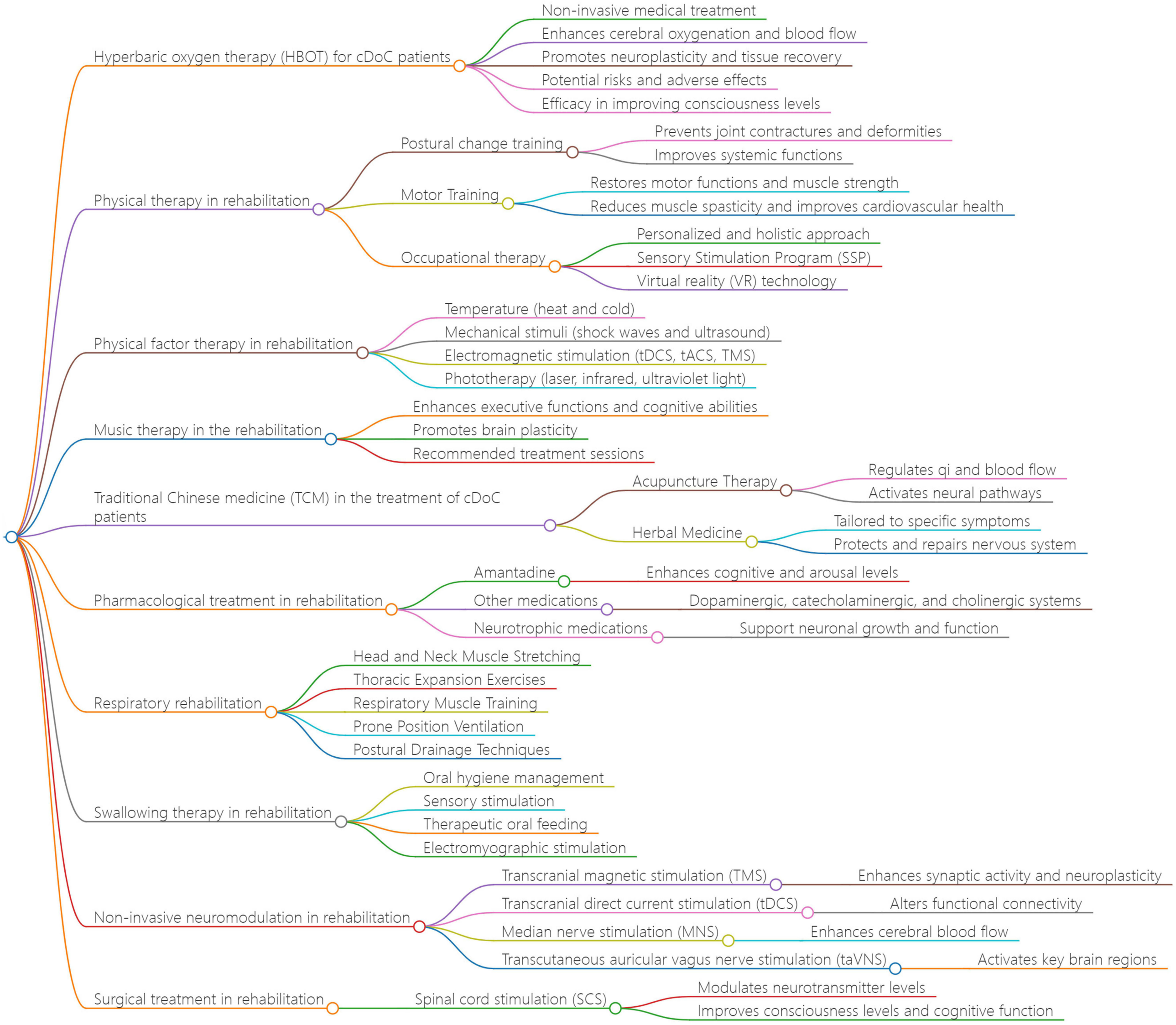

Figure 1 Schematic structure of the Review on multimodal treatment strategies for chronic disorders of consciousness following severe traumatic brain injury.

function, which is crucial for energy production and neuronal repair. Additionally, HBOT reduces oxidative stress and inflammation, contributing to the stabilization of the blood-brain barrier and reduction of cerebral edema. It also decreases capillary permeability, thus minimizing secondary injury processes such as vasogenic edema.[25,27] One of the key benefits of HBOT in neurological conditions is its ability to improve microcirculation. The therapy promotes the regeneration of damaged blood vessels, enhances blood flow to hypoxic brain regions, and stimulates angiogenesis. It also activates the brainstem reticular activating system (RAS), which is vital for maintaining consciousness and cognitive function. By promoting neuronal regeneration and enhancing synaptic plasticity, HBOT aids in the reconnection of disrupted neural networks, offering potential improvements in motor and cognitive outcomes.[22,28] HBOT has also shown efficacy in patients with cDoC, such as those in a vegetative or minimally conscious state. Clinical trials have indicated that HBOT improves cerebral microcirculation and restores oxygen homeostasis, particularly in regions associated with consciousness, such as the thalamus and brainstem. Moreover, HBOT has been found to stimulate the reticular activating system and enhance neural circuit activity, thereby aiding in arousal and recovery of consciousness in some patients. A systematic review of studies on HBOT for cDoC found that approximately 40% of patients demonstrated improvements in consciousness levels following treatment.[29,30]

Despite these benefits, HBOT is not without risks, and its application must be approached with caution. It is contraindicated in individuals with conditions such as unstable hemodynamics, untreated pneumothorax, severe pulmonary infections, pulmonary bullae, and uncontrolled epilepsy, as these conditions may be exacerbated by increased pressure or oxygen levels. Adverse effects of HBOT, though relatively rare, include oxygen toxicity, barotrauma to the lungs and ears, and seizures induced by hyperoxia. While there is a growing body of evidence supporting the efficacy of HBOT in treating neurological and other conditions, further high-quality, multicenter randomized controlled trials (RCTs) are necessary to establish optimal treatment protocols. Current research suggests that HBOT can improve neurological outcomes in patients with sTBI, with studies reporting a 25–30% improvement in Glasgow Coma Scale (GCS) scores following treatment compared to control groups.[25,31] In addition, HBOT has been shown to reduce intracranial pressure and improve functional outcomes, as evidenced by improvements in Glasgow Outcome Scale (GOS) scores and cognitive assessments.[32] However, the precise frequency, duration, and combination of HBOT with other therapies, such as pharmacological interventions and rehabilitation programs, remain areas for further investigation.[33]

Physical Therapy in Rehabilitation

Postural Change Training

Postural change training is an integral part of the rehabilitation process for cDoC patients, especially those who are bedridden and unable to actively participate in recovery efforts (Figure 1 and Table S1). Research has shown that up to 75% of patients with chronic immobilization experience joint contractures, which can lead to permanent disabilities if left untreated.[34,35] This rehabilitation method is essential not only for preventing such complications but also for improving patient arousal levels and increasing eye-opening times. Postural change training stretches joints, muscles, and soft tissues such as tendons, thereby reducing the risk of contractures and deformities, which occur in an estimated 40–60% of bedridden cDoC patients.[34,36] In addition to musculoskeletal benefits, postural change training promotes the recovery of systemic functions, including cardiovascular, pulmonary, and gastrointestinal systems, by enhancing circulation and reducing the risks associated with chronic immobility, such as deep vein thrombosis (DVT), which has an incidence rate of 20–30% in immobilized patients.[37,38] This training also helps prevent orthostatic hypotension, a condition affecting approximately 50% of patients undergoing long-term rehabilitation.

Professional guidance is essential when performing postural changes, as patients need to be transitioned between positions, such as from lying to sitting or sitting to standing, in a controlled manner. This process not only improves blood circulation but also mitigates muscle atrophy, which can reduce by 1–3% per day in immobilized patients.[39,40] Postural changes also enhance spatial orientation and balance, promoting adaptation to daily activities. A progressive approach is recommended, starting with 30 minutes of out-of-bed time per day and gradually increasing to 2–3 hours, eventually aiming for 6–8 hours daily. Studies suggest that increasing daily out-of-bed time can reduce the risk of pressure ulcers by 30% and improve cognitive outcomes in patients with cDoC.[41,42]

While postural change training has demonstrated efficacy in rehabilitation, further research is needed to determine its optimal application across various patient populations, particularly in patients with severe cardiovascular or pulmonary conditions. For those with unresolved postural hypotension, unhealed fractures, heterotopic ossification, severe pain, or significant spasms, postural change training may need to be modified or deferred. Approximately 25–35% of patients with sTBI suffer from such complications, necessitating a more cautious approach.[43]

Motor Training

Motor training is a critical aspect of rehabilitation for cDoC patients and has been shown to significantly improve functional outcomes (Figure 1 and Table S1). Motor training encompasses a range of exercises, from passive to active movements, and aims to restore motor functions, enhance muscle strength, and prevent complications such as disuse muscle atrophy. Muscle atrophy can occur rapidly in immobilized patients, with an estimated 30–40% decrease in muscle mass occurring within the first month of inactivity.[44,45] Therefore, early intervention with motor training is crucial.

Passive joint mobilization exercises, often performed by therapists or mechanical devices, are used to maintain joint flexibility and muscle elasticity in patients who are unable to initiate movements on their own. These exercises are essential in preventing contractures, which develop in up to 45% of patients with chronic immobilization. Active-assisted and active exercises gradually involve the patient, encouraging them to participate and eventually perform movements independently. These exercises enhance neuromuscular coordination and stimulate neuroplasticity, promoting the reorganization of brain networks that are critical for motor recovery. Neuroplasticity is particularly vital for cDoC patients, as evidence suggests that 40–60% of these patients experience some degree of brain network disruption following severe brain injury.[46]

Regular motor training, typically performed for 20–30 minutes per session, 4–6 times per week, has been shown to significantly reduce muscle spasticity in cDoC patients. A randomized controlled trial demonstrated a 25–30% reduction in spasticity among patients undergoing regular motor training.[47] Furthermore, motor training has been shown to promote cardiovascular and respiratory health by improving circulation and lung function, reducing the risk of complications such as pneumonia, which affects approximately 25–40% of patients with prolonged bed rest. Studies have also shown that motor training can reduce the incidence of pressure ulcers by up to 50%, making it a crucial component of comprehensive rehabilitation.[27,48,49] It is essential to carefully assess each patient's condition before initiating motor training, particularly those with unstable medical conditions, such as paroxysmal autonomic hyperactivity, pressure ulcers, or open wounds. Approximately 12–29% of patients with severe traumatic brain injury experience autonomic dysfunction, which can complicate motor training.[50] For these patients, the training regimen should be adjusted to avoid exacerbating their condition.

Motor training, as a non-pharmacological approach, has proven effective in enhancing recovery following sTBI. When combined with early, intensive rehabilitation and HBOT, motor training can lead to significant improvements in cognitive function, motor skills, and the ability to perform daily living activities. A clinical study demonstrated that patients who received combined HBOT and motor training showed a 30–40% improvement in motor function and a 20–25% increase in cognitive recovery, compared to those receiving standard rehabilitation alone.[51] These findings underscore the importance of integrating motor training into the overall rehabilitation strategy for cDoC patients.

Occupational Therapy in Rehabilitation

Occupational therapy plays a critical role in the rehabilitation of patients with cDoC, offering a personalized and holistic approach designed to address their physical, cognitive, and social needs (Figure 1 and Table S1). Through the use of the Occupational Therapy Practice Framework (OTPF), therapists conduct comprehensive assessments, which may include family interviews, cognitive interventions, task-based activities, environmental modifications, and the implementation of assistive technologies. These assessments ensure that therapy is tailored to each patient's unique condition, which can significantly improve functional outcomes. Studies suggest that 40–60% of cDoC patients who receive personalized occupational therapy interventions show measurable improvements in functional independence.[52,53]

A widely used intervention in occupational therapy is the Sensory Stimulation Program (SSP), which involves repetitive multi-sensory stimulation through various modalities, including visual, auditory, olfactory, gustatory, tactile, and vestibular stimuli. Sensory stimulation has been shown to enhance arousal and behavioral responses in cDoC patients. Clinical trials have demonstrated that multi-sensory stimulation can increase arousal levels in up to 35–50% of patients in a vegetative state.[54] For instance, combining HBOT with aromatherapy has been found to effectively improve cognitive function recovery in sTBI patients, with 20–30% of patients showing cognitive improvement after such combined interventions.[52,55]

In addition, virtual reality (VR) technology has emerged as a promising tool in occupational therapy. By integrating VR with music therapy and memory therapy, therapists can provide an immersive Sensory Stimulation Program (SSP) that enhances patient engagement. Evidence shows that 50–60% of patients who undergo VR-based interventions demonstrate enhanced sensory processing and cognitive recovery.[55,56] These interventions have also been associated with improvements in neuroplasticity, which is vital for the recovery of cognitive and motor functions in cDoC patients. Occupational therapy also incorporates environmental adaptations, functional training, cognitive support, and social participation activities. For example, daily living skills training, such as grooming and feeding, are used to restore patients' independence in their activities of daily living (ADLs). This functional recovery is crucial, as studies indicate that 30–40% of cDoC patients regain partial independence in basic ADLs after structured occupational therapy programs.[57] Moreover, sensory activation therapies, such as music therapy and tactile therapy, are used to stimulate the sensory systems and promote neuroplasticity, fostering the reorganization of neural networks and functional recovery. Research has shown that sensory activation can improve overall rehabilitation outcomes in 25–35% of patients with severe brain injuries.[58]

Despite its benefits, occupational therapy interventions should be applied cautiously in patients with unstable vital signs or those unable to tolerate such interventions. For example, patients with severe autonomic dysfunction, which occurs in up to 15–20% of cDoC patients, may require modified treatment approaches.[58,59] Furthermore, specific sensory stimulation activities, such as olfactory or auditory stimuli, should be adjusted according to each patient's tolerance level to avoid overstimulation, which could exacerbate autonomic instability in certain cases. By integrating these diverse approaches, occupational therapy not only helps patients regain essential daily living skills but also promotes their overall recovery and quality of life. Studies have reported that patients participating in occupational therapy, particularly those involving sensory stimulation, show improvements in cognitive and motor functions, with 45–55% of cDoC patients achieving better engagement and rehabilitation outcomes after therapy.[60] Additionally, early intervention has been linked to better long-term outcomes, further emphasizing the critical role of occupational therapy in the comprehensive management of cDoC patients.

Physical Factor Therapy in Rehabilitation

Physical factor therapy encompasses various modalities, including temperature (heat and cold), mechanical stimuli (such as shock waves and ultrasound), electromagnetic stimulation (including magnetotherapy, direct current, low-frequency and mid-frequency currents, and high-frequency currents), and phototherapy (laser, infrared, and ultraviolet light) (Figure 1 and Table S1). These approaches serve as vital treatment methods for addressing a range of clinical issues in patients with cDoC.[61,62] Transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) are particularly noteworthy within the realm of electrical stimulation therapy. By modulating the membrane potential of neurons, these techniques adjust neuronal excitability and promote neuroplasticity in the brain. Studies indicate that tDCS can lead to a 30–50% improvement in consciousness levels and cognitive functions among patients with traumatic brain injuries.[63] Additionally, tACS has been associated with enhanced cognitive performance, showing effects on memory and attention in up to 40% of patients.[64]

Another promising modality is transcranial magnetic stimulation (TMS), which utilizes magnetic fields to induce electrical currents in the cortical regions of the brain. This method has demonstrated potential for improving consciousness levels in patients suffering from acquired brain injuries, with evidence showing 25–35% of participants experiencing clinically significant improvements.[65,66] The development and application of physical factor therapy are continually evolving, aided by advancements in neuroimaging and electrophysiological techniques, which facilitate the effective design of rehabilitation interventions.[67] Although the mechanisms of action and optimal intervention parameters for these therapies remain under investigation, future research must consider the balance between the specificity of stimulation targets, invasiveness, and patient acceptability. Personalized rehabilitation strategies should be tailored to the unique needs of individual patients, taking into account their specific conditions and responses to treatment. These therapies act directly on the nervous system, modulating neuronal activity and facilitating the recovery of impaired brain regions. Emerging data suggest that physical factor therapies can significantly enhance recovery outcomes, with a reported 20–40% increase in functional improvement for patients who engage in comprehensive rehabilitation programs that incorporate these modalities.[67,68]

Music Therapy in the Rehabilitation

Music therapy, a non-pharmacological intervention, has demonstrated efficacy in enhancing executive functions, improving cognitive abilities, and promoting brain plasticity through the activation of critical neural networks (Figure 1 and Table S1). These effects are particularly beneficial for patients with cDoC, aiding in the elevation of awareness levels.[69,70] To achieve optimal therapeutic outcomes, it is crucial that music selection is tailored to the individual preferences of the patient. Involving family members or certified music therapists in this selection process ensures that the music chosen holds therapeutic value and resonates emotionally with the patient. Evidence suggests that live performances by professional music therapists provide a deeper, more immersive experience, fostering a stronger connection and engagement.[71] Recommended treatment sessions typically last between 10 to 15 minutes, with a frequency of at least twice daily. This regimen helps prevent overstimulation and fatigue, which can hinder the therapeutic process.[72] Research has shown that consistent music therapy can lead to a 20–30% improvement in cognitive responsiveness and engagement among cDoC patients.[72] Despite its potential benefits, caution is warranted in patients who exhibit unstable vital signs or those who are unable to tolerate this type of intervention. In such cases, it may be necessary to modify the approach or seek alternative therapeutic modalities.

Traditional Chinese Medicine (TCM) in the Treatment of cDoC Patients

Traditional Chinese Medicine (TCM) has a long-standing history and diverse schools of thought in the treatment of patients with cDoC, particularly in the neurological recovery of patients suffering from sTBI (Figure 1 and Table S1). TCM employs various therapeutic modalities, with acupuncture and herbal medicine being the primary methods utilized.[73]

Acupuncture Therapy

Acupuncture aims to awaken consciousness and restore neurological function. For patients exhibiting excessive conditions (shi syndrome), acupuncturists typically select points such as Renzhong (GV26), Neiguan (PC6), and Hegu (LI4) for rapid needle manipulation or electrical stimulation. Each session lasts approximately 10 to 20 minutes, with treatment courses spanning 7 to 10 days.[74,75] For patients with deficient conditions (xu syndrome), characterized by symptoms like malnutrition or anemia, points such as Qihai (CV6) and Zusanli (ST36) are often targeted using tonifying techniques. Moxibustion may be applied to points like Baihui (GV20), Shenque (CV8), and Guanyuan (CV4) to enhance vitality.[76,77] The mechanisms of acupuncture involve regulating qi and blood flow, activating neural pathways, and inducing anti-inflammatory responses, which facilitate local blood circulation and repair of damaged neural tissues. Evidence-based studies have shown that the integration of the “Awakening Brain Needling” technique with HBOT can significantly enhance brain tissue functionality and promote neural repair.[78]

Herbal Medicine

Herbal treatment in TCM is tailored to the specific symptoms of the patient (Figure 1 and Table S1). For patients with high fever associated with excess conditions, formulas such as An Gong Niu Huang Wan are often utilized. In the absence of high fever, Su He Xiang Wan is recommended, alongside other decoctions like Bu Yang Huan Wu Tang and Hua Yu Tong Qiao Fang, with modifications based on the individual condition. In some cases, herbal decoctions may be administered rectally to clear heat and alleviate constipation.[73,79] These herbal formulations aim to harmonize the balance of qi and blood within the body, and their active components have demonstrated protective and reparative effects on the nervous system.[80,81] Study indicates that patients with a minimally conscious state (MCS) who receive HBOT combined with herbal treatments to invigorate qi and activate blood circulation show significant improvements in consciousness levels and daily functional capabilities.[82] Future studies should continue to explore optimal applications of TCM in conjunction with modern medical therapies to enhance treatment efficacy and improve patient quality of life. However, caution should be exercised in administering TCM therapies to patients with unstable vital signs or those who may not tolerate such interventions.[73,83]

Pharmacological Treatment in Rehabilitation

Pharmacological treatment plays an indispensable role in the rehabilitation of patients with sTBI (Figure 1 and Table S1). Evidence-based research has revealed that amantadine, administered at daily doses ranging from 200 to 400 mg, significantly enhances cognitive and arousal levels in patients suffering from traumatic brain injuries.[84,85] This pharmacological intervention is therefore strongly recommended in the treatment protocols for sTBI. In addition to amantadine, other medications targeting dopaminergic, catecholaminergic, and cholinergic systems, such as zolpidem and baclofen, have been utilized in clinical practice. However, the effectiveness and safety of these treatments require further investigation to establish their clinical applicability.[86] In particular, neurotrophic medications, including methylcobalamin, aminopyridine, and B-vitamins, have demonstrated the potential to support neuronal growth and function, thereby promoting the repair and regeneration of neural tissue.[87,88] These agents play a crucial role in enhancing neuroplasticity and facilitating recovery in patients with sTBI. However, while these drugs show promising prospects in clinical settings, further studies are necessary to determine the optimal treatment regimens, including dosages and the potential for synergistic effects when combined with other therapeutic modalities.

Respiratory Rehabilitation

Respiratory rehabilitation is a critical method for improving pulmonary function in patients with cDoC (Figure 1 and Table S1). This rehabilitation encompasses a comprehensive array of exercises and techniques designed to enhance lung ventilation and oxygen utilization efficiency. Key components of respiratory rehabilitation include: 1) Head and Neck Muscle Stretching: Targeting the upper respiratory muscles to improve airway patency. 2) Thoracic Expansion Exercises: Promoting chest wall mobility and increasing tidal volume. 3) Respiratory Muscle Training: Utilizing devices such as inspiratory muscle trainers to enhance diaphragm and intercostal muscle strength. 4) Prone Position Ventilation: Enhancing lung perfusion and ventilation, particularly in patients with acute respiratory distress. 5) Postural Drainage Techniques: Assisting in the clearance of respiratory secretions through gravity-assisted positioning. These interventions not only improve lung function but also reduce the risk of respiratory infections, facilitate weaning from mechanical ventilation, and enhance the clearance of bronchial secretions. Techniques such as manual chest percussion, vibratory therapy, and postural drainage are particularly beneficial for patients with excess sputum production. Additionally, neuromuscular electrical stimulation (NMES) devices can be utilized to bolster the strength and endurance of respiratory muscles, making them especially useful for patients who have been reliant on mechanical ventilation for extended periods.[89,90]

Respiratory rehabilitation has a dual benefit; it not only aids in restoring respiratory function but also promotes the reorganization of brain neural networks and enhances neuroplasticity through increased muscular activity.[91] This connection underscores the importance of a holistic approach to rehabilitation, integrating respiratory care with neurological recovery. However, the application of respiratory rehabilitation should be approached with caution in patients with severe comorbidities such as significant cardiac arrhythmias, unstable angina, severe hypertension, epilepsy, pneumothorax, or unresolved thoracic fractures. The suitability of these interventions should be carefully evaluated on a case-by-case basis.[92] Treatment duration and frequency should be personalized based on the patient's specific condition and response to therapy, with guidance from a specialized rehabilitation team. As research in rehabilitation medicine advances, it is anticipated that novel methods will emerge to further enhance the rehabilitation outcomes for patients with sTBI and cDoC.[93]

Swallowing Therapy in Rehabilitation

Swallowing therapy plays a crucial role in the rehabilitation of patients with cDoC, particularly those with sTBI (Figure 1 and Table S1). Dysphagia is prevalent among these patients, and the presence of tracheostomy or endotracheal intubation can exacerbate this condition, making swallowing training essential for safe extubation.[94,95] In patients in a vegetative state, the accumulation of pharyngeal secretions and the limited frequency of voluntary swallowing can lead to a heightened risk of aspiration, even when receiving enteral nutrition via nasogastric tube. Therefore, appropriately intensified swallowing therapy is vital to increase the frequency of voluntary swallows and enhance swallowing function.[95]

The foundation for effective swallowing therapy involves comprehensive pre-treatment assessments, including swallowing function evaluations and endoscopic examinations. These assessments guide the development of individualized treatment plans, which typically encompass: 1) Oral hygiene management: Ensuring proper oral care to minimize the risk of aspiration pneumonia. 2) Sensory stimulation: Incorporating temperature, tactile, and flavor stimuli to promote swallowing reflexes. 3) Therapeutic oral feeding: Gradual introduction of oral feeding, focusing on safe swallowing techniques. 4) Electromyographic stimulation: Utilizing electrical stimulation to enhance muscle activity involved in swallowing.[96] For patients deemed suitable for oral feeding, monitoring and adjustment of food textures are critical. The use of thickeners can significantly reduce the risk of aspiration, ensuring a safer feeding process.[97] However, for those with unstable vital signs or who cannot tolerate swallowing exercises, caution is necessary in implementing these interventions. Research indicates that the combination of oral-pharyngeal therapy (OPT) with HBOT has demonstrated significant improvements in cerebral oxygen metabolism and swallowing function in affected patients, while also reducing serum biomarkers associated with neuronal damage.[98] This integrative approach underscores the potential of multi-modal rehabilitation strategies to enhance recovery outcomes in patients with cDoC. Although swallowing therapy is an indispensable component of rehabilitation for cDoC patients, requiring careful assessment and personalized treatment plans to ensure safety and efficacy. Continued exploration of combined therapeutic modalities may further optimize rehabilitation strategies in this patient population.[95,98]

Non-Invasive Neuromodulation in Rehabilitation

Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) utilizes electromagnetic pulses to enhance synaptic activity in the cerebral cortex (Figure 1 and Table S1). By modulating cortical excitability, TMS promotes neuroplasticity and holds potential therapeutic effects for patients with chronic consciousness disorders. The most widely applied TMS protocol is Repetitive Transcranial Magnetic Stimulation (rTMS), particularly high-frequency rTMS (≥5 hz), which increases the excitability of targeted cortical regions, thereby facilitating arousal.[99] This method is primarily used to stimulate the Dorsolateral Prefrontal Cortex (DLPFC) and Posterior Parietal Cortex (PPC), typically with stimulation intensities set at 80% to 100% of the resting motor threshold, delivering 1000 to 1500 pulses per session over a course of 1 to 20 days.[99] Evidence suggests that the combined application of HBOT and high-frequency rTMS not only enhances consciousness levels but also improves neurophysiological activity, thereby mitigating the extent of brain injury.[100] Additionally, Intermittent Theta Burst Stimulation (iTBS) is recognized as an effective TMS mode, improving overall cognitive function in chronic consciousness disorder patients with more pronounced benefits. However, TMS should be used cautiously in patients with unstable lesions at the target site, a history of epilepsy, skull defects at the treatment location, or implanted metallic devices (eg, ventilators, metallic tracheostomy tubes), as these conditions may affect the safety and efficacy of the treatment.

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a safe, non-invasive method of physical stimulation for the brain, well-tolerated by patients (Figure 1 and Table S1). Research indicates that tDCS positively impacts arousal treatment in chronic consciousness disorder patients by altering the functional connectivity of the frontoparietal network.[101] Key to achieving therapeutic effects is selecting the appropriate stimulation target, typically the DLPFC, primary sensory-motor cortex, and anterior frontal regions. Treatment protocols generally consist of 20-minute sessions with a current density set at 40–56 µA/cm², administered daily for 10 consecutive days, with the option for one to two additional treatment courses based on patient response. Caution is advised when administering tDCS to patients with intracranial metallic implants, as this may compromise treatment safety and efficacy. A comprehensive assessment of the patient's medical history and physical condition is essential prior to initiating tDCS therapy.

Median Nerve Stimulation (MNS)

Median nerve stimulation (MNS) involves stimulating the median nerve to transmit nerve impulses to the brainstem, thalamus, and cerebral cortex, aiming to enhance cerebral blood flow, activate the brainstem reticular system, and increase cortical excitability[102,103] (Figure 1 and Table S1). Research indicates that treatment is typically applied to the dominant side, with parameters set at a frequency of 40 hz, current strength of 10–20 mA, and pulse width of 300 ms, with stimulation lasting 20–30 seconds per minute for 3–8 hours daily over a two-week treatment cycle.[103] The combination of right median nerve stimulation with HBOT significantly improves brain tissue oxygenation and blood flow in traumatic brain injury patients, facilitating neurological recovery.[104] Adverse reactions to this treatment are rare; however, it should be approached cautiously in patients with skin lesions or infections at the stimulation site and in those unable to tolerate the procedure. A thorough evaluation of the patient is required before MNS therapy to ensure safety and effectiveness.

Transcutaneous Auricular Vagus Nerve Stimulation (taVNS)

Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive brain stimulation technique that stimulates the auricular branch of the vagus nerve[104] (Figure 1 and Table S1). This stimulation may activate key brain regions such as the nucleus tractus solitarius and the ascending reticular activating system, subsequently influencing salient networks, the limbic system, and interoceptive systems, thus enhancing cortical excitability and potentially aiding the recovery of consciousness in affected patients. Typical stimulation sites include the concha and cymba of the ear, with parameters usually set at a frequency of 20–25 hz, current intensity of 1–6 mA, and pulse width less than 1000 µs. Treatment generally involves 1–2 sessions daily, with each session lasting 30 minutes over a duration of 4–8 weeks. Although taVNS shows promise in facilitating consciousness recovery, further research is needed to explore its maximum therapeutic effects under specific conditions.[104] Care should be taken with patients who have skin lesions or infections at the stimulation site, as well as those who cannot tolerate the treatment.

Surgical Treatment in Rehabilitation

In the management of patients with cDoC following sTBI, surgical awakening techniques have emerged as significant therapeutic interventions (Figure 1 and Table S1). These techniques primarily include percutaneous puncture short-duration spinal cord stimulation (SCS) and open cervical posterior approach long-duration spinal cord stimulation.[105] Stimulation therapy typically commences within 48 hours post-operation, employing intermittent pulse current release to modulate neurotransmitter levels, such as dopamine and norepinephrine, in brain regions associated with arousal.[105] Research indicates that the application of SCS can lead to improvements in consciousness levels, with some studies reporting up to a 40% increase in patients transitioning from a vegetative state to a minimally conscious state.[105] A meta-analysis encompassing multiple studies on SCS for cDoC patients revealed that approximately 35–60% of treated individuals exhibit a measurable increase in arousal and cognitive function post-stimulation.[106] Furthermore, a longitudinal study demonstrated that 45% of patients who underwent SCS exhibited sustained improvements in consciousness over a follow-up period of 6 months.[107] These findings underscore the potential of SCS as a viable therapeutic option in the rehabilitation process for cDoC patients. Clinical practice has demonstrated the potential of these surgical methods to improve consciousness levels in cDoC patients, providing a robust treatment option that can significantly impact patient outcomes. Nonetheless, patient selection criteria remain crucial, as those with stable neurological conditions and favorable prognostic indicators tend to benefit most from such interventions.[108]

Discussion

This review examines multimodal rehabilitation strategies and their clinical outcomes for patients with chronic disorders of consciousness (cDoC). The findings highlight that the integrated use of various treatment modalities significantly improves patient prognosis, particularly when hyperbaric oxygen therapy (HBOT) is applied in combination with other rehabilitation approaches. HBOT facilitates consciousness recovery by enhancing cerebral oxygenation and blood flow, as well as activating the brainstem reticular activating system. When paired with physical training and occupational therapy, patients show a 30–40% improvement in motor function and cognitive abilities. However, the efficacy of HBOT is influenced by factors such as individual variability, treatment timing, and duration, indicating the need for further research to identify optimal treatment protocols.

In the realm of foundational rehabilitation therapies, posture change training and physical exercise offer a range of clinical benefits. These interventions not only prevent complications but also promote recovery in circulatory, respiratory, and digestive system functions. Notably, posture change training plays a key role in preventing joint contractures and deep vein thrombosis. Successful implementation of these treatments requires precise, individualized assessments, especially for patients with autonomic dysfunction or pressure ulcers, underlining the importance of personalized treatment plans. Occupational therapy integrates sensory stimulation and technologies such as virtual reality to provide tailored rehabilitation for patients. Studies indicate that approximately 40–60% of patients show functional improvement after personalized occupational therapy. However, its effectiveness is closely tied to the patient's baseline condition, necessitating a cautious, individualized approach, particularly for those with unstable autonomic function.

https://doi.org/10.2147/IJGM.S502086

Neuroregulatory therapies, including transcranial electrical stimulation (tDCS) and transcranial magnetic stimulation (TMS), demonstrate promise in modulating cortical excitability to promote functional recovery. Traditional Chinese medicine therapies, such as acupuncture, have shown potential in activating brain neural functions and improving blood circulation, though further rigorous randomized controlled trials are required to establish their clinical efficacy. Additionally, certain specialized interventions, such as music therapy and respiratory rehabilitation, often underappreciated, have demonstrated significant potential in fostering neurological recovery. Music therapy activates brain neural networks and supports cognitive function recovery, though further research is needed to define optimal personalized music selection. Respiratory rehabilitation not only improves the physiological condition of patients but also may positively influence the remodeling of brain neural networks. Swallowing therapy is an essential rehabilitation component, with its effectiveness often dependent on the patient's specific condition and the timing of intervention. Electrophysiological stimulation has been shown to be more effective in early interventions, while long-term coma patients may experience limited benefits due to local neural damage.

In particular, patients with cDoC following severe traumatic brain injury often face communication difficulties, which impact their quality of life and caregiving outcomes. With advancements in technology, emerging tools such as eye-tracking, brain-computer interfaces (BCI), and neuroimaging have provided new ways for these patients to communicate.[109,110] Eye-tracking allows patients to respond to questions by focusing on specific targets, while neuroimaging helps assess their conscious state.[111] BCIs can directly interpret brain signals, enabling patients to express their needs and emotions.[112] These technological advancements not only improve communication but also promote personalized diagnosis and treatment, offering new hope for the care and rehabilitation of patients with chronic TBI.

Overall, based on the current research and advancements in technology, future studies should focus on the following key areas: first, the development of more precise treatment parameters, including frequency, intensity, and duration; second, the exploration of optimal combinations of therapeutic methods to maximize synergistic effects; third, the creation of an enhanced evaluation system for accurate monitoring of treatment outcomes and timely adjustments; and finally, large-scale randomized controlled trials to assess the long-term safety and efficacy of various interventions.

Conclusion

This review highlights the multimodal treatment approaches for cDoC patients following sTBI, emphasizing the positive impact of therapies like HBOT, physical therapy, and occupational therapy. These interventions have proven effective in improving consciousness and neurological recovery. However, further research is needed to optimize these treatments. Key areas include the development of personalized treatment plans based on genetic markers, standardization of assessment tools, better understanding of biological mechanisms, long-term follow-up studies, and integration of technologies such as VR and AI. These advancements can improve patient outcomes and provide more accessible, effective rehabilitation. Recovery from sTBI-related cDoC is a medical and societal challenge that requires collaboration across healthcare systems. With ongoing advancements, the outlook for these patients is promising, offering opportunities for more comprehensive and humane care.

Acknowledgments

We thank all the authors for their active participation in this study, contributing to literature collection, organization, valuable suggestions, and manuscript writing.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the "Guangdong High-level Hospital Construction Fund and Sanming Project of Medicine in Shenzhen (No. SZSM202011012)", "Shenzhen Fund for Guangdong Provincial High-level Clinical Key Specialties (No. SZXK035)", and "Shenzhen Science and Technology Program (No. JCYJ20230807093804010)".

Disclosure

The authors report no conflicts of interest in this work.

References

1. Varghese R, Chakrabarty J, Menon G. Nursing management of adults with severe traumatic brain injury: a narrative review. *Indian J Crit Care Med*. 2017;21(10):684. doi:10.4103/ijccm.IJCCM_233_17
2. Zrelak PA, Eigsti J, Fetzick A, et al. Evidence-based review: nursing care of adults with severe traumatic brain injury. *Am Assoc Neurosci Nurses*. 2020;42:1–42.
3. Oyesanya TO, Bowers BJ, Royer HR, Turkstra LS. Nurses' concerns about caring for patients with acute and chronic traumatic brain injury. *J Clin Nurs*. 2018;27(7–8):1408–1419. doi:10.1111/jocn.14298
4. Nguyen A, Nguyen A, Hsu TI, et al. Neutrophil to lymphocyte ratio as a predictor of postoperative outcomes in traumatic brain injury: a systematic review and meta-analysis. *Diseases*. 2023;11(1):51. doi:10.3390/diseases11010051
5. Marino MA, Siddiqi I, Maniakhina L, et al. Neurosurgical outcomes in severe traumatic brain injuries between service lines: review of a single institution database. *Cureus*. 2023;15(4).
6. Olesen J, Gustavsson A, Svensson M, et al. The economic cost of brain disorders in Europe. *Eur J Neurol*. 2012;19(1):155–162. doi:10.1111/j.1468-1331.2011.03590.x
7. Giacino JT, Katz DI, Schiff ND, et al. Comprehensive systematic review update summary: disorders of consciousness: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Neurology*. 2018;91(10):461–470. doi:10.1212/WNL.0000000000005928
8. Carlson JM, Lin DJ. Prognostication in prolonged and chronic disorders of consciousness. In: *Seminars in Neurology*. Thieme Medical Publishers, Inc.; 2023.
9. Aloi D, Della Rocchetta AI, Ditchfield A, Coulborn S, Fernández-Espejo D. Therapeutic use of transcranial direct current stimulation in the rehabilitation of prolonged disorders of consciousness. *Front Neurol*. 2021;12:632572. doi:10.3389/fneur.2021.632572
10. Delargy M, O'Connor R, McCann A, Galligan I, Cronin H, Gray D. O'Toole C: an analysis of the effects of using Zolpidem and an innovative multimodal interdisciplinary team approach in prolonged disorders of consciousness (PDOC). *Brain Injury*. 2019;33(2):242–248. doi:10.1080/02699052.2018.1537008
11. Kondziella D, Bender A, Diserens K, et al. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. *Eur J Neurol*. 2020;27(5):741–756. doi:10.1111/ene.14151
12. Schnakers C, Vanhaudenhuyse A, Giacino J, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol*. 2009;9:1–5. doi:10.1186/1471-2377-9-35
13. Wang J, Hu X, Hu Z, Sun Z, Laureys S, Di H. The misdiagnosis of prolonged disorders of consciousness by a clinical consensus compared with repeated coma-recovery scale-revised assessment. *BMC Neurol*. 2020;20:1–9. doi:10.1186/s12883-020-01924-9
14. Haddad AR, Lythe V, Green AL. Deep brain stimulation for recovery of consciousness in minimally conscious patients after traumatic brain injury: a systematic review. *Neuromodulation*. 2019;22(4):373–379. doi:10.1111/ner.12944
15. Wilde EA, Wanner I-B, Kenney K, et al. A framework to advance biomarker development in the diagnosis, outcome prediction, and treatment of traumatic brain injury. *J Neurotrauma*. 2022;39(7–8):436–457. doi:10.1089/neu.2021.0099
16. Mosilhy EA, Alshial EE, Eltaras MM, et al. Non-invasive transcranial brain modulation for neurological disorders treatment: a narrative review. *Life Sci*. 2022;307:120869. doi:10.1016/j.lfs.2022.120869
17. Chen R, Huang L, Wang R, Fei J, Wang H, Wang J. Advances in non-invasive neuromodulation techniques for improving cognitive function: a review. *Brain Sci*. 2024;14(4):354. doi:10.3390/brainsci14040354
18. Pekdemir B, Raposo A, Saraiva A, et al. Mechanisms and potential benefits of neuroprotective agents in neurological health. *Nutrients*. 2024;16(24):4368. doi:10.3390/nu16244368
19. Dong X, Tang Y, Zhou Y, Feng Z. Stimulation of vagus nerve for patients with disorders of consciousness: a systematic review. *Front Neurosci*. 2023;17:1257378. doi:10.3389/fnins.2023.1257378
20. Tekmyster G, Jonely H, Lee DW, et al. Physical therapy considerations and recommendations for patients following spinal cord stimulator implant surgery. *Neuromodulation*. 2023;26(1):260–269. doi:10.1111/ner.13391
21. Lim JA-O, Li J, Zhou M, Xiao X, Xu Z. Machine learning research trends in traditional Chinese medicine: a bibliometric review. *Int J Gene Med*. 2024;Volume 17:5397–5414. [1178-7074 (Print)]. doi:10.2147/IJGM.S495663
22. Yan L, Liang T, Cheng O. Cheng O: hyperbaric oxygen therapy in China. *Med Gas Res*. 2015;5(1):1–6. doi:10.1186/s13618-015-0024-4
23. Lam G, Fontaine R, Ross FL, Chiu ES. Chiu ES: hyperbaric oxygen therapy: exploring the clinical evidence. *Adv Skin Wound Care*. 2017;30(4):181–190. doi:10.1097/01.ASW.0000513089.75457.22
24. Grim PS, Gottlieb LJ, Boddie A, Batson E. Hyperbaric oxygen therapy. *JAMA*. 1990;263(16):2216–2220. doi:10.1001/jama.1990.03440160078042
25. Huang L, Obenaus A. Obenaus A: hyperbaric oxygen therapy for traumatic brain injury. *Med Gas Res*. 2011;1(1):1–7. doi:10.1186/2045-9912-1-21
26. Kalani M, Jörneskog G, Naderi N, Lind F, Brismar K. Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers: long-term follow-up. *J diabet complicat*. 2002;16(2):153–158. doi:10.1016/S1056-8727(01)00182-9

27. Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med*. 2002;347(14):1057–1067. doi:10.1056/NEJMoa013121
28. Dong Z, Yang Z, Gao X. Therapeutic effect of hyperbaric oxygen therapy on acute cerebral infarction and its influence on neuro-logical function, blood oxygen saturation, levels of M-CSF, ox-LDL and sICAM-1. *Chin J cardiovasc Rehab Med*. 2019;56–59.
29. Rockswold SB, Rockswold GL, Zaun DA, Liu J. A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. *J Neurosurg*. 2013;118(6):1317–1328. doi:10.3171/2013.2.JNS121468
30. Ortega MA, Fraile-Martinez O, García-Montero C, et al. A general overview on the hyperbaric oxygen therapy: applications, mechanisms and translational opportunities. *Medicina*. 2021;57(9):864. doi:10.3390/medicina57090864
31. McDonagh M, Helfand M, Carson S, Russman BS. Hyperbaric oxygen therapy for traumatic brain injury: a systematic review of the evidence. *Arch Phys Med Rehabil*. 2004;85(7):1198–1204. doi:10.1016/j.apmr.2003.12.026
32. Efrati S, Fishlev G, Bechor Y, et al. Hyperbaric oxygen induces late neuroplasticity in post stroke patients-randomized, prospective trial. *PLoS One*. 2013;8(1):e53716. doi:10.1371/journal.pone.0053716
33. Jain KK, Baydin S. *Textbook of Hyperbaric Medicine*. 2017.
34. Pistarini C, Maggioni G. Early rehabilitation of disorders of consciousness (DOC): management, neuropsychological evaluation and treatment. *Neuropsychological Rehabilitat*. 2018;28(8):1319–1330. doi:10.1080/09602011.2018.1500920
35. Seel RT, Douglas J, Dennison AC, Heaner S, Farris K, Rogers C. Specialized early treatment for persons with disorders of consciousness: program components and outcomes. *Arch Phys Med Rehabil*. 2013;94(10):1908–1923. doi:10.1016/j.apmr.2012.11.052
36. Zemková E, Kováčiková Z. Sport-specific training induced adaptations in postural control and their relationship with athletic performance. *Front Human Neurosci*. 2023;16:1007804. doi:10.3389/fnhum.2022.1007804
37. Zahia S, Zapirain MBG, Sevillano X, González A, Kim PJ, Elmaghraby A. Pressure injury image analysis with machine learning techniques: a systematic review on previous and possible future methods. *Artif. Intell. Med.* 2020;102:101742. doi:10.1016/j.artmed.2019.101742
38. McLendon K, Goyal A, Attia M. Deep venous thrombosis risk factors. 2017.
39. Boussi-Gross R, Golan H, Fishlev G, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury-randomized prospective trial. *PLoS One*. 2013;8(11):e79995. doi:10.1371/journal.pone.0079995
40. Saxon SV, Etten MJ, Perkins EA. *RNLD F: Physical Change and Aging: A Guide for Helping Professions*. Springer Publishing Company; 2021.
41. Zhang B, Karri J, O'Brien K, DiTommaso C, Kothari S, Li S. Spasticity management in persons with disorders of consciousness. *Pm&r*. 2021;13(7):657–665. doi:10.1002/pmrj.12458
42. Martens G, Laureys S, Thibaut A. Spasticity management in disorders of consciousness. *Brain Sci*. 2017;7(12):162. doi:10.3390/brainsci7120162
43. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol*. 2008;7(8):728–741. doi:10.1016/S1474-4422(08)70164-9
44. Laurent H, Aubreton S, Richard R, et al. Coudeyre E: systematic review of early exercise in intensive care: a qualitative approach. *Anaesth Crit Care Pain Med*. 2016;35(2):133–149. doi:10.1016/j.accpm.2015.06.014
45. McDonnell MN, Smith AE, Mackintosh SF. Aerobic exercise to improve cognitive function in adults with neurological disorders: a systematic review. *Arch Phys Med Rehabil*. 2011;92(7):1044–1052. doi:10.1016/j.apmr.2011.01.021
46. Muller AM, Meyerhoff DJ. Maladaptive brain organization at 1 month into abstinence as an indicator for future relapse in patients with alcohol use disorder. *Eur. J. Neurosci.* 2021;53(8):2923–2938. doi:10.1111/ejn.15161
47. Sahin N, Ugurlu H, Albayrak I. The efficacy of electrical stimulation in reducing the post-stroke spasticity: a randomized controlled study. *Disability Rehabil*. 2012;34(2):151–156. doi:10.3109/09638288.2011.593679
48. Regan MA, Teasell RW, Wolfe DL, Keast D, Mortenson WB, Aubut J-AL. Team SCIRER: a systematic review of therapeutic interventions for pressure ulcers after spinal cord injury. *Arch Phys Med Rehabil*. 2009;90(2):213–231. doi:10.1016/j.apmr.2008.08.212
49. DeJong G, Hsieh C-HJ, Brown P, et al. Factors associated with pressure ulcer risk in spinal cord injury rehabilitation. *Am J Phys Med Rehabil*. 2014;93(11):971–986. doi:10.1097/PHM.0000000000000117
50. Singh J, Lanzarini E, Santosh P. Organic features of autonomic dysregulation in paediatric brain injury–Clinical and research implications for the management of patients with Rett syndrome. *Neurosci Biobehav Rev.* 2020;118:809–827. doi:10.1016/j.neubiorev.2020.08.012
51. Jöhr J, Halimi F, Pasquier J, Pincherle A, Schiff N, Diserens K. Recovery in cognitive motor dissociation after severe brain injury: a cohort study. *PLoS One*. 2020;15(2):e0228474. doi:10.1371/journal.pone.0228474
52. Zasler ND, Katz DI, Zafonte RD. *Brain Injury Medicine: Principles and Practice*. Demos Medical Publishing; 2012.
53. Langan B, Lin K. 19 Brain Injury-Related Spasticity: a Case-Based Approach. In: *Handbook of Spasticity.* 2023.
54. Lombardi FF, Taricco M, De Tanti A, Telaro E, Liberati A, Group CI. Sensory stimulation for brain injured individuals in coma or vegetative state. *Cochrane Database Syst Rev.* 1996;2010(1).
55. Katz N, Association AOT. *Cognition, occupation, and participation across the life span: neuroscience, neurorehabilitation, and models of intervention in occupational therapy.* 2011.
56. Aida J, Chau B, Dunn J. Immersive virtual reality in traumatic brain injury rehabilitation: a literature review. *NeuroRehabilitation*. 2018;42(4):441–448. doi:10.3233/NRE-172361
57. Giacino JT. Rehabilitation of patients with disorders of consciousness. In: *Rehabilitation for Traumatic Brain Injury.* New York: Oxford University Press; 2005:305–337.
58. Wilson BA, Winegardner J, van Heugten C, Ownsworth T. *Neuropsychological Rehabilitation: The International Handbook*. Psychology Press; 2017.
59. Wijdicks EF, Kramer AH. Critical care neurology part I: neurocritical care. *Elsevier.* 2017.
60. Furl J. Occupational Therapy Interventions for Patients with Disorders of Consciousness (DOC). 2024.
61. Galea MP. Physical modalities in the treatment of neurological dysfunction. *Clin. Neurol. Neurosurg.* 2012;114(5):483–488. doi:10.1016/j.clineuro.2012.01.009
62. Evancho A, Tyler WJ, McGregor K. A review of combined neuromodulation and physical therapy interventions for enhanced neurorehabilitation. *Front Human Neurosci*. 2023;17:1151218. doi:10.3389/fnhum.2023.1151218

63. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*. 2000;527(Pt 3):633. doi:10.1111/j.1469-7793.2000.t01-1-00633.x
64. Antal A, Paulus W. Transcranial alternating current stimulation (tACS). *Front Human Neurosci*. 2013;7:317. doi:10.3389/fnhum.2013.00317
65. Kuo M-F, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage*. 2014;85:948–960. doi:10.1016/j.neuroimage.2013.05.117
66. Brunoni AR, Sampaio-Junior B, Moffa AH, et al. Noninvasive brain stimulation in psychiatric disorders: a primer. *Brazilian Journal of Psychiatry*. 2018;41:70–81. doi:10.1590/1516-4446-2017-0018
67. Chen L, Hudaib A-R, Hoy KE, Fitzgerald PB. Efficacy, efficiency and safety of high-frequency repetitive transcranial magnetic stimulation applied more than once a day in depression: a systematic review. *J Affective Disorders*. 2020;277:986–996. doi:10.1016/j.jad.2020.09.035
68. Taye WA. A review of the evolution and advancements of neurological physical therapy. *J Biomed Sustain Healthcare Appl*. 2024;63–72. doi:10.53759/0088/JBSHA20240407
69. Bradt J, Dileo C. Music interventions for mechanically ventilated patients. *Cochrane Database Syst Rev*. 2014;2018(12). doi:10.1002/14651858.CD006902.pub3
70. Jia T, Ogawa Y, Miura M, Ito O, Kohzuki M. Music attenuated a decrease in parasympathetic nervous system activity after exercise. *PLoS One*. 2016;11(2):e0148648. doi:10.1371/journal.pone.0148648
71. Schumacher K. Music therapy for pervasive developmental disorders, especially autism. The music in music therapy: psychodynamic music therapy in Europe. *Clin, Theoret Res Approach*. 2014;107–123.
72. Pakdeesatitwara N, Tamplin J. Music therapy services in neurorehabilitation: an international survey. *Aust J Music Ther*. 2018;29:62–90.
73. Lee B, Leem J, Kim H, Jo H-G, Kwon C-Y. Herbal medicine for traumatic brain injury: a systematic review and meta-analysis of randomized controlled trials and limitations. *Front Neurol*. 2020;11:772. doi:10.3389/fneur.2020.00772
74. Rabinstein AA, Shulman LM. Acupuncture in clinical neurology. *Neurologist*. 2003;9(3):137–148. doi:10.1097/00127893-200305000-00002
75. Zhang J-H, Wang D, Liu M. Overview of systematic reviews and meta-analyses of acupuncture for stroke. *Neuroepidemiology*. 2013;42(1):50–58. doi:10.1159/000355435
76. G-t H, Wang Y. Advances in treatment of post-traumatic stress disorder with Chinese medicine. *Chin J Integr Med*. 2021;27(11):874–880. doi:10.1007/s11655-021-2864-1
77. Ren -J-J, Tian H-C, Wang Y-F, Li Y-T, Xu Q, Tian L. Effectiveness and safety of moxibustion for poststroke insomnia: a systematic review and meta-analysis. *World J Traditional Chin Med*. 2022;8(2):199–209. doi:10.4103/2311-8571.335136
78. Tan L, Zeng L, Wang N, et al. Acupuncture to promote recovery of disorder of consciousness after traumatic brain injury: a systematic review and meta-analysis. *Evid Based Complementary Altern Med*. 2019;2019(1):5190515. doi:10.1155/2019/5190515
79. Lee B, Leem J, Kim H, et al. Herbal medicine for acute management and rehabilitation of traumatic brain injury: a protocol for a systematic review. *Medicine*. 2019;98(3):e14145. doi:10.1097/MD.0000000000014145
80. Wei C, Wang J, Yu J, et al. Therapy of traumatic brain injury by modern agents and traditional Chinese medicine. *ChinMed*. 2023;18(1):25. doi:10.1186/s13020-023-00731-x
81. Panahi Y, Rajaee SM, Johnston TP, Sahebkar A. Neuroprotective effects of antioxidants in the management of neurodegenerative disorders: a literature review. *J Cell Biochem*. 2019;120(3):2742–2748. doi:10.1002/jcb.26536
82. Ye Q-Y, Lin Q, Hu X-L, et al. Efficacy and safety of combined Chinese and Western medicine in the treatment of knee osteoarthritis: a prospective, multicenter cohort study. *Front Pharmacol*. 2023;14:1176980. doi:10.3389/fphar.2023.1176980
83. Liu B-G, Xie M, Dong Y, et al. Antimicrobial mechanisms of traditional Chinese medicine and reversal of drug resistance: a narrative review. *Eur. Rev. Med. Pharmacol. Sci*. 2022;26(15).
84. Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med*. 2012;366(9):819–826. doi:10.1056/NEJMoa1102609
85. Meythaler JM, Brunner RC, Johnson A, Novack TA. Amantadine to improve neurorecovery in traumatic brain injury–associated diffuse axonal injury: a pilot double-blind randomized trial. *J Head Trauma Rehabil*. 2002;17(4):300–313. doi:10.1097/00001199-200208000-00004
86. Peppel LD, Ribbers GM, Heijenbrok-Kal MH. Pharmacological and non-pharmacological interventions for depression after moderate-to-severe traumatic brain injury: a systematic review and meta-analysis. *J Neurotrauma*. 2020;37(14):1587–1596. doi:10.1089/neu.2019.6735
87. Sawangjit R, Thongphui S, Chaichompu W, Phumart P. Efficacy and safety of mecobalamin on peripheral neuropathy: a systematic review and meta-analysis of randomized controlled trials. *J Altern Complementary Med*. 2020;26(12):1117–1129. doi:10.1089/acm.2020.0068
88. Onose G, Daia-Chendreanu C, Haras M, Ciurea A, Anghelescu A. Traumatic brain injury: current endeavours and trends for neuroprotection and related recovery. *Romanian Neurosurg*. 2011;11–30.
89. Salman GF, Mosier MC, Beasley BW, Calkins DR. Rehabilitation for patients with chronic obstructive pulmonary disease: meta-analysis of randomized controlled trials. *J Gen Intern Med*. 2003;18:213–221. doi:10.1046/j.1525-1497.2003.20221.x
90. Osadnik CR, Rodrigues FM, Camillo CA, et al. Principles of rehabilitation and reactivation. *Respiration*. 2015;89(1):2–11. doi:10.1159/000370246
91. Xu C, Yang F, Wang Q, Gao W. Effect of neuromuscular electrical stimulation in critically ill adults with mechanical ventilation: a systematic review and network meta-analysis. *BMC Pulm Med*. 2024;24(1):56. doi:10.1186/s12890-024-02854-9
92. Mary P, Servais L, Vialle R. Neuromuscular diseases: diagnosis and management. *Orthop Traumatol*. 2018;104(1):S89–S95.
93. McNamara RJ, Dale M, McKeough ZJ. Innovative strategies to improve the reach and engagement in pulmonary rehabilitation. *J Thoracic Dis*. 2019;11(Suppl 17):S2192. doi:10.21037/jtd.2019.10.29
94. Alhashemi HH. Dysphagia in severe traumatic brain injury. *Neurosci J*. 2010;15(4):231–236.
95. Sharma OP, Oswanski MF, Singer D, et al. Swallowing disorders in trauma patients: impact of tracheostomy. *Am Surg*. 2007;73(11):1117–1121. doi:10.1177/000313480707301107
96. Bhattacharyya N. The prevalence of dysphagia among adults in the United States. *Otolaryngol Head Neck Surg*. 2014;151(5):765–769. doi:10.1177/0194599814549156
97. Yang Y, Xu J, Sang -T-T, Wang H-Y. A review and evidence based recommendations on starch-and gum-based thickeners for dysphagic patients: proper thickeners for dysphagic patients. *J Food Meas Charact*. 2022;16(4):3140–3152.

98. Ni -X-X, Nie J, Xie Q-Y, Yu R-H, Su L, Liu Z-F. Protective effects of hyperbaric oxygen therapy on brain injury by regulating the phosphorylation of Drp1 through ROS/PKC pathway in heatstroke rats. *Cell Mol Neurobiol*. 2020;40(8):1253–1269. doi:10.1007/s10571-020-00811-8
99. Torii T, Sato A, Nakahara Y, Iwahashi M, Itoh Y, Iramina K. Frequency-dependent effects of repetitive transcranial magnetic stimulation on the human brain. *Neuroreport*. 2012;23(18):1065–1070. doi:10.1097/WNR.0b013e32835afaf0
100. Hallett M. Transcranial magnetic stimulation and the human brain. *Nature*. 2000;406(6792):147–150. doi:10.1038/35018000
101. Lefaucheur J-P, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol*. 2017;128(1):56–92. doi:10.1016/j.clinph.2016.10.087
102. Guerra A, Maria Costantini E, Maatta S, Ponzo D, Ferreri F. Disorders of consciousness and electrophysiological treatment strategies: a review of the literature and new perspectives. *Curr. Pharm. Des*. 2014;20(26):4248–4267.
103. Feller D, Vinante C, Trentin F, Innocenti T. Innocenti T: the effectiveness of median nerve electrical stimulation in patients with disorders of consciousness: a systematic review. *Brain Injury*. 2021;35(4):385–394. doi:10.1080/02699052.2021.1887522
104. Bremner JD, Wittbrodt MT, Gurel NZ, et al. Transcutaneous vagal nerve stimulation in trauma spectrum psychiatric disorders. *Vagus Nerve Stimulation*. 2023;157–184.
105. Si J, Dang Y, Zhang Y, et al. Spinal cord stimulation frequency influences the hemodynamic response in patients with disorders of consciousness. *Neurosci. Bull*. 2018;34:659–667. doi:10.1007/s12264-018-0252-4
106. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology*. 2002;58(3):349–353. doi:10.1212/WNL.58.3.349
107. Bender A, Jox RJ, Grill E, Straube A, Lulé D. Persistent vegetative state and minimally conscious state: a systematic review and meta-analysis of diagnostic procedures. *Dtsch Arztebl Int*. 2015;112(14):235. doi:10.3238/arztebl.2015.0235
108. Riganello F, Cortese M, Arcuri F, et al. A study of the reliability of the nociception coma scale. *Clin rehabilitat*. 2015;29(4):388–393. doi:10.1177/0269215514546767
109. Rakkolainen I, Farooq A, Kangas J, et al. Technologies for multimodal interaction in extended reality—a scoping review. *Multimodal Technol Inter*. 2021;5(12):81. doi:10.3390/mti5120081
110. Casado-Aranda LA, Sánchez-Fernández J, Bigne E, Smidts A. The application of neuromarketing tools in communication research: a comprehensive review of trends. *Psychol Marketing*. 2023;40(9):1737–1756. doi:10.1002/mar.21832
111. Wolf A, Ueda K. Contribution of eye-tracking to study cognitive impairments among clinical populations. *Frontiers in Psychology*. 2021;12:590986. doi:10.3389/fpsyg.2021.590986
112. Houssein EH, Hammad A, Ali AA. Human emotion recognition from EEG-based brain–computer interface using machine learning: a comprehensive review. *Neural Comput Appl*. 2022;34(15):12527–12557. doi:10.1007/s00521-022-07292-4