Published in final edited form as:

Curr Phys Med Rehabil Rep. 2016 March ; 4(1): 56–70.

A Narrative Review of Pharmacologic and Non-pharmacologic Interventions for Disorders of Consciousness Following Brain Injury in the Pediatric Population

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Abstract

Traumatic brain injury (TBI) is the most common cause of long-term disability in the United States. A significant proportion of children who experience a TBI will have moderate or severe injuries, which includes a period of decreased responsiveness. Both pharmacological and non-pharmacological modalities are used for treating disorders of consciousness after TBI in children. However, the evidence supporting the use of potential therapies is relatively scant, even in adults, and overall, there is a paucity of study in pediatrics. The goal of this review is to describe the state of the science for use of pharmacologic and non-pharmacologic interventions for disorders of consciousness in the pediatric population.

Keywords

Pharmacologic; Non-pharmacologic; Disorders of consciousness; Brain injury; Traumatic brain injury; Pediatrics

Introduction

Traumatic brain injury (TBI) is the most common cause of long-term disability in the United States. Over 6000 children and adolescents age 19 years and younger are killed annually by TBI, and over 60,000 are admitted to the hospital for treatment after TBI [1]. The economic impact of pediatric TBI in the United States is estimated between \$1 and \$1.5 billion for direct medical costs during the 12 months after injury [2, 3]. About 15 % of children who experience a TBI will have moderate or severe injuries that include a period of decreased responsiveness [4]. Longer time to recovery from disorders of consciousness is predictive of worse prognosis after TBI [5, 6], and some reports suggest that shortening the period of

Conflict of Interest Brad G. Kurowski declares grants from the NIH. Nathan K. Evanson and Andrea L. Paulson declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

disordered consciousness may improve outcomes, at least in part by increasing participation in rehabilitation treatment [7, 8].

The pathobiology of disorders of consciousness is related to abnormalities in brain function; however, structural changes are also observed [9]. Disorders of consciousness are associated with a 40–50 % reduction of global brain metabolism compared to healthy individuals [10, 11]. Imaging studies have identified structural changes primarily in the cerebral cortex and thalamus associated with disorders of consciousness, implicating disruption of the cortico-thalamic network as a primary pathobiological mechanism [9, 12, 13]. The use of both pharmacological and non-pharmacological modalities targeting the pathobiology of disorders of consciousness is common in clinical care. However, there is a small evidence base for treating disorders of consciousness in adults [14, 15], and the evidence in children is more sparse [7, 16]. Overall, the evidence for pharmacological treatment is stronger in children than for non-pharmacological interventions. Previous review articles have addressed neuropharmacology and pharmaceutical interventions following brain injuries in children, but have not focused specifically on disorders of consciousness or have not included non-pharmacological interventions [7, 16]. The goal of this review is to describe the state of the science for use of pharmacological and non-pharmacological interventions in managing decreased responsiveness and disorders of consciousness in the pediatric population after brain injury.

Pharmacological Interventions

In 184 adults aged 16–65 years who were in a vegetative or minimally conscious state following TBI, a large, multi-center, randomized clinical trial demonstrated use of amantadine following severe TBI accelerated functional recovery over the first 4–16 weeks after injury [17]. Pharmacologic studies of a similar magnitude and rigor have not been conducted in the pediatric population. However, several smaller studies have been performed. Most of these smaller studies evaluated dopamine agonists (i.e., increase dopamine release or block dopamine reuptake) that are thought to potentiate neurotransmitter systems damaged after TBI and are important in mediating attention, behavioral initiation, and alertness [18, 19]. The other common class of medication evaluated is gamma-aminobutyric acid (GABA) agonists (e.g., zolpidem). Although GABA agonists are typically thought to depress the central nervous system, use of these agents is hypothesized to reverse the condition of GABA impairment encountered after TBI, thus restoring the balance between synaptic excitation and inhibition in the injured brain [20]. Below is a summary of studies evaluating the use of pharmacologic interventions for decreased responsiveness and disorders of consciousness in the pediatric population. More detailed information on study methodology and results is found in Table 1.

Dopaminergic Medications

The most well-studied medication for disorders of consciousness following a brain injury in the pediatric population is amantadine. In 2004, a retrospective case–controlled study evaluated the use of amantadine in 54 children, ages 3–18 years. Outcomes included change in Rancho Los Amigos Score (Rancho score), length of post-traumatic amnesia, and length

of hospital stay [21]. Amantadine use at a dose of 400 mg was well tolerated in the majority of participants. Nine percent of study participants had side effects that may have been related to amantadine (hallucinations, delusions, increased aggression, and nausea and vomiting). All reported side effects improved when amantadine was decreased or discontinued. Amantadine was associated with a greater increase in Rancho score compared to the control group ($p < 0.01$). There was no difference in length of hospital stay or length of post-traumatic amnesia between the two groups. In a randomized, double-blind placebo-controlled crossover trial, five children 2–12 weeks after injury with disordered consciousness were randomized to placebo or amantadine for three weeks, followed by a one week washout period and then crossover to the other agent for three weeks [22]. The half-life of amantadine is 13–17 h, therefore five half-lives (assuming 17 h each) are 85 h or 3.5 days, and a one week washout period appears adequate in terms of systemic circulation. Longer-term biologic effects on transcription and receptor expression after a three week treatment period in this population are unclear. The maximum dose for amandine was 6 mg/kg with a cap at 400 mg daily, divided into two doses. Outcome measures included the coma near coma scale and coma recovery scale—revised. Each scale was completed three times a week. Weekly pediatric functional independence measure (Wee-FIM) scores and subjective report of level of consciousness by parents and attending physician were also used. There was no significant difference in the slopes of recovery for amantadine or placebo on the coma near coma scale, coma recovery scale—revised or Wee-FIM (although with only five subjects, this study is likely underpowered to find such a difference). However, the weekly subjective report by parents and physicians revealed positive improvements in level of consciousness during amantadine use periods ($p = 0.02$). The authors concluded that amantadine facilitates recovery of consciousness. A follow-up study of the same population assessed the pharmacokinetics of amantadine [23]. The authors concluded that amantadine at 6 mg/kg/day up to a maximum dose of 400 mg/day was overall well tolerated in children with brain injury, with only one child experiencing vomiting as a side effect, and pharmacokinetics were similar to healthy controls. No routine drug monitoring is recommended based on this study.

Two additional studies evaluated dopamine-enhancing medications for treatment of disorders of consciousness following brain injury in children. There was large variability in the dopamine agents used, including methyl-phenidate, pramipexole, amantadine, bromocriptine, and levodopa [24, 25]. The first study was a retrospective review including ten children who were at least 30 days post-injury. The study used rate of change on the Western neurosensory stimulation profile (WNSSP) as the primary outcome. Children taking a dopamine-enhancing medication improved faster on the WNSSP, suggesting a positive relationship between the dopamine-enhancing medication and acceleration of recovery. Medications were taken for a minimum of 43 days. The second study was a prospective randomized, double-blind, double-baseline study of pramipexole or amantadine in ten children who were at least four weeks post-injury. Participants underwent dosage increases over four weeks and were weaned over the following three weeks. Outcome measures were the WNSSP, coma near coma scale, disabilities rating scale, and change in Rancho score. Improvement from baseline was noted on all scales in both groups without a clear statistical

difference in efficacy between amantadine and pramipexole, and no serious adverse effects were noted.

Benefits of methylphenidate were assessed in a retrospective chart review of ten children following brain injury. Two had disorders of consciousness and the remaining eight had more mild injury (based on Rancho score of four or greater) as well as behavioral concerns [26]. Outcome measures were pre- and post-intervention behaviors as documented by parents, teachers, and the treatment team. Individuals with mild injuries who started at a Rancho score of seven had improved attention, impulsivity, and activity levels. The one individual with Rancho score of four had improved agitation, attention, and participation in therapies. Individuals with a Rancho score of three had a slight increase in responsivity and arousal when on medication compared to when the medication was held. The authors concluded that there was subjective improvement in all participants with some effects in the participants with disorders of consciousness; however, long-term benefits were unclear.

GABAergic Medications

A prospective double-blind placebo-controlled randomized study assessed benefits of zolpidem (0.14–0.2 mg/kg) or placebo on a total of three participants, two with hypoxic-ischemic injury and one with a traumatic injury. The participants were given the medication for four days followed by ten days without medication, then four days of the other agent [27]. Outcome measures were the Rancho score, coma near coma scale, and positron emission tomography (PET) scan imaging (to look at cerebral glucose metabolism as a possible marker of increased brain activity). The authors found no change in the Rancho score, a non-significant worsening on the coma near coma scale when on zolpidem, and no change in parent report of behavior or PET scan. The authors concluded that zolpidem was associated with a tendency toward a more reduced responsive state in children with disorders of consciousness, although based on an approximately 5 % response rate in adults [28•], this study is likely underpowered to find individuals who would respond to zolpidem treatment.

Non-pharmacological Interventions

In addition to pharmacological treatments for disorders of consciousness, there are a number of other treatment modalities that have been evaluated. Most of these are based on sensory or nervous system stimulation, but there are also several studies investigating regenerative medicine modalities. These studies are summarized below and more detailed information on study methodology, and results can be found in Table 2. These modalities are not well studied, and most of the literature that is available includes primarily adults. Due to the paucity of literature on children, studies have been included in our discussion when they have included any pediatric participants. In some cases, pediatric results have been separated from adult results, but in many of these studies, results have been analyzed together. However, because of the exploratory nature of this section, we have included these results as well.

Sensory Stimulation

Most studies of sensory stimulation involving children have used multimodal approaches. None of these studies have been of high quality. There are several protocols described for providing sensory stimulation, but in general, these protocols attempt to stimulate all or most of the primary senses (auditory, visual, tactile, sometimes taste, smell, and/or proprioception).

An observational cohort study of children and adolescents using a protocol known as “Snoezelen” (a controlled multisensory stimulation approach, delivered in a specially designed therapy room) showed consistent improvement in Rancho scores over a three week period [29]. There was no control group, so the role of natural recovery is not clear. Another small clinical trial that included several older adolescents showed decreased length of coma with multimodal sensory stimulation compared to matched controls [30]. In contrast, a cohort study using multimodal sensory stimulation, with a historical control group, showed no statistically significant improvement in time to recovery from coma or Glasgow Outcome Scale scores [31]. This study included both pediatric and adult participants (ages 6–75 years). One case series using “musico-kinetic therapy” to treat mostly adults, included a 14-year-old female who had a full recovery of consciousness, as measured by a clinical persistent vegetative state score [32]. The therapy protocol involved bouncing on a trampoline in supported sitting, in time with music, thus involving vestibular, tactile, and auditory stimulation. Another “case series with meta-analysis,” including a participant as young as 12 years old (individual ages were not reported), showed greater improvements (such as increase in total time with eyes open) with multimodal, personally salient stimulation, compared to unimodal stimulation [33]. Unimodal stimulation consisted of random selection of a single sense to stimulate for each session. Based on the design and information reported from this study, it is unclear how these findings translate to broader functional outcomes. A small clinical study ($n = 4$), including two children using “sensory regulation,” showed improved Rancho and Glasgow coma scale (GCS) scores compared to matched controls [34]. “Sensory regulation” consisted of controlling the timing and types of stimuli given, rather than just providing increased sensory stimulation. This approach is proposed to target the sensory stimulation to an individual’s needs after brain injury, but not overwhelm the limited sensory processing capacity seen after brain injury. Finally, in a single-case report of a 16-year old given auditory stimulation alone, there was increased arousal by physiological measures such as heart rate, but there was not a clinical return of consciousness [35].

Electrophysiology

Various electrophysiological stimulation methods have been investigated, although there are no published high-quality studies, particularly in children. Methods with some evidence of efficacy in children or adolescents include median nerve electrical stimulation, dorsal column spinal electrical stimulation, transcranial direct current and magnetic stimulation, and deep brain stimulation. These methods involve electrical stimulation, either of peripheral sites, or directly of the brain. In general, these stimulation modalities are thought to alter circuit-level neuronal signaling (such as changing relative levels of excitatory and inhibitory signaling) [36–38], or increase general arousal by stimulating lower parts of the brain such

as the reticular activating system or basal ganglia [39–41]. There is also evidence that local electrical fields are established during development and recapitulated during recovery from brain injury, and that these electrical fields may influence recovery [42].

One of the least invasive of the electrophysiologic methods is median nerve stimulation. This approach is done by electrically stimulating the median nerve using surface electrodes [43]. One unblinded, controlled study that included children as young as six years showed improved outcomes (measured by Glasgow Coma Scale and functional independence measure scores) at six months in median nerve stimulation compared to usual care [44]. On a case series level, several adolescents [43] and a 12-year old [41] demonstrated improvement in level of consciousness after median nerve stimulation.

Dorsal column spinal cord stimulation was investigated for treating disorders of consciousness after Kanno et al. noted that individuals with spastic hemiplegia being treated using this modality also sometimes had improvements in their EEG [45]. This observation led to trialing stimulation in a case series of individuals with persistent vegetative state. Stimulation of the dorsal columns of the spinal cord (at the approximately C2–C4 level) was found to be potentially effective [46]. There were three of five children/adolescents and young adults in the 5–25-year old range (exact ages were not given) that showed improvement to the point of following commands.

Non-invasive stimulation of the brain has also been attempted using transcranial magnetic stimulation and transcranial direct current stimulation. Both of these approaches are thought to work at least in part by altering cortical excitation [47–49]. As in other modalities, the evidence for efficacy in children is limited. In a case series of adults in a vegetative or minimally conscious state, one participant who was 19 years old at the time of study (13 years at time of injury) showed improvement on the coma recovery scale—revised from eight (vegetative state) to nine (minimally conscious) over 12 months after initiation of stimulation [47]. Similarly, a case series of adults in a vegetative state after TBI included a 19-year old who was about seven months post-injury [50]. Several individuals in the study, including the 19-year-old adolescent, had improved command following and increased motor-evoked potential amplitude during transcranial magnetic stimulation when they were asked to imitate movements performed by the examiner.

An invasive electrical stimulation protocol known as deep brain stimulation, which has been used for movement disorders such as dystonia [51] has also been proposed as a treatment for disorders of consciousness. This proposal is based on early theories that activation of subcortical brain regions such as the brainstem, thalamus, and basal ganglia (including the reticular activating system) leads to cortical activation [39, 40, 52]. Evidence for deep brain stimulation is largely confined to physiologic data without associated behavioral recovery [53], and a single subject study in an adult who had improvement in the level of consciousness [36, 54]. There was a single-case series published using thalamic stimulation, which included children [55]. Individual results were not reported in this series, but children as young as five years were included. Approximately half of the study population (13/25) showed improvement in their neurologic exam over the course of three months. There was

no control group for comparison. Because there is a significant rate of spontaneous recovery during this time period [53], this complicates the analysis of this series.

Regenerative

Regenerative medicine involves regrowing or regenerating damaged tissue with the goal of restoring normal function [56]. In the case of disordered consciousness after TBI, this approach involves an attempt to regenerate damaged brain tissue that is contributing to a vegetative or minimally conscious state. While there are few data available, there is limited evidence that stem cell transplantation or hyperbaric oxygen treatment may lead to regeneration with functional recovery.

Stem cell transplantation therapy has produced promising effects in preclinical research [57–59]. It is postulated to act through several possible mechanisms, including production of trophic factors, direct cell-to-cell interactions, and functional differentiation and integration into host neuronal circuits [59]. Evidence for cell transplantation in children is limited to two case series [60, 61], both of which were largely in adults. Individuals who showed no recovery of consciousness 5–8 weeks post-injury were transplanted with fetal brain cells and liver hematopoietic cells from aborted (spontaneous or induced) fetuses. The first series [60] included one 17-year-old male and one 18-year-old female, both of whom had significant recovery after transplantation. Follow-up brain imaging (by MRI) demonstrated reversal of early brain atrophy, six months post-transplant in the 18-year old. These results were reportedly typical for this study (33 of 38 cases showed recovery of a conscious state, usually within three to seven days after the last treatment). Interestingly, a group of adults with hypoxic injury also received transplants but did not show improvement in their level of consciousness [61].

Hyperbaric oxygen therapy, on the other hand, is felt to work through multiple mechanisms. In the early period after injury, it decreases cerebral blood flow while improving oxygen delivery and decreasing intracranial pressure [62]. In the longer term after injury, there is evidence from animal studies for reduced gliosis and increased neuron content in the hippocampus [63]. As with other therapies for TBI, there is limited evidence for its use in children after TBI. In a retrospective chart review in which three individuals under age 18 were included, there was significant recovery in individuals with persistent vegetative state, as measured by GCS, Rancho scores, and disability rating scale scores [64]. A larger clinical trial that included adolescents as young as 12 years showed significant improvements in post-TBI symptoms [65]. However, this study involved milder TBI, and disorders of consciousness were not investigated. It should be noted that after TBI in adults, hyperbaric oxygen treatment is controversial, largely due to concerns about oxygen toxicity and overall safety of the treatment [62]. Also, there have been mixed results of adult clinical trials, with some studies showing lack of improvement [66] and others showing improvement in functional and metabolic end points [67].

Conclusions

The state of evidence for treatment of disorders of consciousness after TBI in children is poor. There is an extreme paucity of literature evaluating pharmacologic and non-

pharmacologic interventions, and the literature is further limited by small sample sizes in the few prospective studies and retrospective reports or case-control studies performed. Additionally, the wide variation in medications and other treatments studied, etiologies of brain injury included, and outcome measures used make comparisons difficult. Even though there are multiple prospective trials, a true meta-analysis is not possible due to the variation in outcome measures and treatments used. In the adult brain injury literature, there have been additional medications evaluated for disorders of consciousness, including bromocriptine, intrathecal baclofen, and other intrathecal GABA agonists, levodopa, and subcutaneous apomorphine; however, pediatric studies of these agents are lacking. Based on the current literature in pediatric populations, amantadine treatment appears to be well tolerated and has some evidence of benefit, so it may be considered as a first-line treatment. However, larger confirmatory studies of amantadine in the pediatric population are still needed. Other dopamine agonists (such as pramipexole or bromocriptine) could also be considered, but there is little evidence currently to support their safety or efficacy in pediatric populations after TBI. Zolpidem has no evidence of efficacy in the few children with TBI in which it has been tried, although given the low rate of response in adults [28], more study is likely needed before discounting zolpidem as a potential treatment. Although there is some evidence for several other medication treatments for disorders of consciousness after TBI in adults, there is no evidence on these treatments in the pediatric population.

Published studies on the use of modalities for management of disorders of consciousness include primarily case series or uncontrolled trials; therefore, it is difficult to make clear clinical recommendations currently. However, prior work suggests that further research is warranted on many of these modalities. In particular, modalities such as sensory stimulation and median nerve stimulation are potentially attractive because they are relatively easy to perform, and are non-invasive and relatively low-risk. Thus, the risk-benefit profile is favorable even though the evidence for efficacy is very slim.

Because of the potential importance of the dopamine system in recovery after brain and the state of the current evidence, the dopaminergic class of medications, specifically amantadine, has demonstrated the best evidence and should likely be a focus for future research in the pediatric population after brain injury. There is a critical need for larger, multi-center trials to validate the findings of previous pilot studies. It is also critical to consider individual (e.g., age, genetics, and sex) and injury-related factors in addition to other biomarkers of injury and recovery to identify individuals most likely to benefit from certain medications. Furthermore, preclinical trials of childhood brain injury, using well-characterized pediatric TBI and hypoxia models (e.g., [68–70]), are needed to inform future clinical trials for disorders of consciousness in children after brain injury. Multimodal clinical and preclinical trials of pharmacologic and non-pharmacologic modalities should also be considered.

In conclusion, there has been little study regarding the treatment of pediatric disorders of consciousness after TBI. With the exception of amantadine, there is insufficient evidence to make any clear recommendations, and even in that case all that can be said is that it appears to be well tolerated, and may be beneficial. Considering that more rapid recovery from less

responsive states improves readiness for rehabilitation and may improve outcomes [8], more study is clearly needed on this important topic.

Acknowledgments

Funding for this work was supported in part by the National Institute for Child Health and Human Development Grants HD074683 (BGK) and HD001097 (NKE). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or other supporting agencies. The authors have no financial relationships relevant to this article to disclose.

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Pharmacological treatment for disorders of consciousness following pediatric brain injury

Table 1

Authors/title	Study design	Study population/demographics	Intervention	Outcome measures	Results	Conclusions
Snyman 2010/ zolpidem for persistent vegetative state—a placebo-controlled trial in pediatrics	Prospective, double-blind, placebo- controlled, randomized trial	Three children (male 4, 6, and 17 years, two with hypoxic-ischemic injury, one pedestrian vs. MVC) <i>Eligibility</i> PVS > 1 year	Zolpidem (or placebo) 0.14–0.2 mg/kg for 4 days, off for 10 days then repeated	RLCFS CNCS Positron emission tomography	RLCFS no change CNCS tendency to increase with zolpidem PET without significant change Parent observation without change in alertness	Zolpidem associated with a tendency toward a reduced responsiveness in patients with PVS
Patrick 2003/the use of dopamine- enhancing medications with children in low response states following brain injury	Retrospective review	Ten children (8–19 years, mean 13.7 years, seven TBI, one CVA, one anoxia, one encephalitis) <i>Eligibility</i> > 30 days in low response state, (RLCFS I–III)	Four methylphenidate, three pramipexole, three amantadine, one bromocriptine, one levodopa (one bromocriptine and amantadine, one pramipexole and amantadine)	WNSSP two before meds (mean rate change 0.68/day) and three on meds at days 15, 26, 43 (mean rate change 0.89/ day)	Improved WNSSP scores with meds ($p = 0.03$), significant rates of change in WNSSP over time (pre- med vs. on med) p $= 0.02$	Dopamine- enhancing medications suggest a promising relationship in acceleration of recovery in “low response state”
Patrick 2006/ dopamine-agonist therapy in low response children following traumatic brain injury	8-week prospective, randomized, double-baseline and double-blind trial	Ten children (8–21 years, mean 16.7 years), <i>Eligibility</i> > 4 weeks at RLCFS I–III by condition	Pramipexole or amantadine, randomized, stratified (vegetative state or minimally conscious state), in block design. Dose increased over 4 weeks and weaned over 3 weeks	CNCS WNSSP RLCFS DRS	Significant improvement in scores from baseline to medication phase on CNCS, WNSSP and DRS ($p < 0.005$), weekly rate of change better on than off meds for all measures ($P <$ 0.05), RLCFS improved significantly on meds ($p < 0.05$)	No difference in efficacy between amantadine and pramipexole, significant improvements on both, no serious adverse effects
McMahon 2009/ effects of amantadine in children with impaired consciousness caused by acquired brain injury	Randomized, double-blind placebo- controlled crossover trial, 3 weeks med/placebo 1 week washout 3-week other agent	Five children (mean 12.7 years, three trauma, one anoxia, one CVA) <i>Eligibility</i> 5–18 years, 2–12-week post-brain injury and CNCS > 2 signifying a coma, vegetative state or minimally conscious state or inability to follow commands	Amantadine max dose was 6 mg/kg to max of 400 mg divided BID; two- step dosing regimen	CNCS CRS-R Weekly subjective evaluation of arousal and consciousness by MD/parent Weekly Wee-FIM	No significant difference in slopes of recovery during either arm for CNCS or CRS-R ($p = 0.24$, 0.28) or Wee-FIM ($p = 0.33$) Improvements in consciousness noted by	Suggests that amantadine use is tolerated in children and may facilitate recovery of consciousness

Authors/title	Study design	Study population/demographics	Intervention	Outcome measures	Results	Conclusions
Green 2004/ amantadine in pediatric patients with traumatic brain injury: a retrospective, case-controlled study	Retrospective, case-controlled report	54 pts (3–18 years) on amantadine (64 controls) <i>Eligibility</i> 1–18 years, TBI diagnosis, length of stay > 48 h, and started on amantadine for the study group	Amantadine, dosage not given for most patients	Change in RLCFS Length of PTA LOS	physicians during weeks of amantadine ($p =$ 0.02) Only adverse event was vomiting thought to be related to amantadine 5/54 (9 %) with side effects possibly related to amantadine (hallucinations, delusions, increased aggression, N/V —improved with decreased dose/ stopping med) Amantadine group with greater RLCFS increase than control group $p < 0.01$ No difference in LOS or PTA	Amantadine is well tolerated in peds TBI pts Subjective improvements in majority (63 %) of pts receiving amantadine Amantadine group with greater RLCFS improvement during admission
Vargus-Adams 2010/ pharmacokinetics of amantadine in children with impaired consciousness due to acquired brain injury: preliminary findings using a sparse-sampling technique	Randomized, double-blind placebo- controlled crossover trial, sparse sampling for pharmacokinetics	5 children (mean 12.7 years), (three trauma, one anoxia, one CVA), 3 weeks med/placebo 1 week washout 3 weeks other agent <i>Eligibility</i> 5–18 years, 2–12-week post-brain injury and $CNCS > 2$ signifying a coma, vegetative state or minimally conscious state or inability to follow commands	Amantadine max dose was 6 mg/kg upto 400 mg divided BID	CNCS CRS-R Weekly subjective evaluation of arousal and consciousness by MD/parent Weekly Wee-FIM Plasma concentrations of amantadine	Amantadine total body clearance was 0.17L/h/kg with a half-life of 13.9 h Higher exposure of amantadine may be associated with better recovery of consciousness Amantadine at 6 mg/kg/day is well tolerated in children with acquired brain injury and pharmacokinetics similar to those of healthy young adults, higher dosing may be considered in the setting of brain injury N/V in one subject with highest drug concentration Do not recommend clinical drug monitoring	Amantadine at 6 mg/kg/day is well tolerated in children with acquired brain injury and pharmacokinetics similar to those of healthy young adults, higher dosing may be considered in the setting of brain injury N/V in one subject with highest drug concentration Do not recommend clinical drug monitoring
Hornyak 1997/the use of methylphenidate in pediatric traumatic brain injury	Retrospective chart review	10 patients with TBI age 3–16 years (mean 10 + 11, 9 MVC, 1 fall), TBI mild to severe with 2 in minimally responsive state, (7 RLCFS VII, 1 RLCFS IV and 2 RLCFS III)	Methylphenidate	Pre- and post-behaviors were qualitatively assessed based on documented reports by parents, teachers, and treatment team	RLCFS VII's improved attention, impulsivity, and activity level	Subjective improvement in all subjects Some effects in minimally responsive but

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		Eligibility diagnosis of TBI and started on methylphenidate			RLCFS IV improved in agitation, attention, and participation in therapies RLCFS III's slight increase in responsivity and arousal which decreased if drug held	unclear long-term benefit adverse effect was decrease in appetite in one patient
<hr/>						
CNCs coma near coma scale, <i>CRS-R</i> Coma recovery scale—revised, <i>CVA</i> cerebral vascular accident, <i>DRS</i> disability rating scale, <i>LOS</i> length of stay, <i>MD</i> medical doctor, <i>MVC</i> motor vehicle collision, <i>mg</i> milligrams, <i>mg/kg</i> milligrams per kilogram, <i>N/V</i> nausea and vomiting, <i>PET</i> positron emission tomography, <i>PTA</i> post-traumatic amnesia, <i>PVS</i> persistent vegetative state, <i>RLCFS</i> RANCHO levels of cognitive functioning scale, <i>TBI</i> traumatic brain injury, <i>W/NSSP</i> western neurosensory stimulation profile						

Non-pharmacological treatment for pediatric disorders of consciousness following brain injury

Authors/Title	Study design	Study population/demographics	Intervention	Outcome measures	Results	Conclusions
Pediatric studies						
Cooper 2003/ electrical treatment of coma via the median nerve	Retrospective case series	N = 3; 16-year-old female GCS 4, 12-year-old male no GCS reported, 14-year-old female GCS 4. Etiology: 2 = MVC, 1 = pedestrian vs. van	Median nerve stimulation	No standardized measure, observational	All participants showed an improvement in consciousness and were able to resume school activities	Median nerve stimulation seems to be associated with improvement following severe brain injury
Hotz 2006/ Snoezelen: a controlled multisensory stimulation therapy for children recovering from severe brain injury	Observational study	N = 15, Age 1.2–16.9 years, mean 9.87 years, 11 male and five female. Etiology 14 severe TBI (8 pedestrian hit by car, 5 MVC, one near drowning, one motorcycle accident) and one anoxic event. GCS at scene 3–8 mean 4.8	The Snoezelen treatment sessions involved the following phases: (1) introduction to the room, (2) carrying out of the session through equipment use and (3) winding the session down	Physiological measures (HR, SBP, DBP, MAP, O2 SAT and muscle tone (Modified Ashworth Scale)) Rancho scale Agitated behavior scale (ABS) Functional- Independent measure (FIM)	Heart rates significantly decreased for each subject in each treatment session ($p = 0.032$). Muscle tone decreased (right upper extremity p = 0.009, left upper extremity $p =$ 0.020, right lower extremity $p =$ 0.036 and left lower extremity p = 0.018). Agitation levels decreased over time. Cognitive outcome measures significantly improved	Snoezelen therapy may benefit children recovering from severe brain injury
Primarily adult studies						
Angelakis 2014/ transcranial direct current stimulation effects in disorders of consciousness	Prospective, case series trial	N = 10; seven men, three women; age range, 19–62 years; etiology: traumatic brain injury, $n = 5$; anoxia, $n = 4$; postoperative infarct, $n = 1$; duration of PVS or MCS range, 6 months to 10 years	Sham transcranial direct current stimulation (tDCS) for 20 min per day, 5 days per week, for 1 week, and real tDCS for 20 min per day, 5 days per week, for 2 weeks	CRS-R	All participants in an MCS showed clinical improvement immediately after treatment	tDCS seems promising for the rehabilitation of patients with severe disorders of consciousness
Cooper 1999/right median nerve electrical stimulation to hasten awakening from coma	double-blind prospective trial with randomization to treatment or sham	N = 6, 2 male and 4 female, 13–42 years, GCS 4–8 at presentation	8–12 h of stimulation at the right median nerve for 2 weeks or sham stimulation	Change in GCS, number of days in the intensive care unit	Shorter ICU stay in treated patients (7.7 days vs. 17 days) and GCS improvement of 4	Median nerve stimulation seems to be associated with improvement following

Authors/Title	Study design	Study population/demographics	Intervention	Outcome measures	Results	Conclusions
Delia 1993/ electrophysiological evolution of post- traumatic persistent vegetative states under thalamic stimulation	Case series	$N = 25$ severe head injury with initial GCS 3–5, age 5–42 years, PVS for 3 months without improvement	Thalamic deep brain stimulation	EEG measures	vs. 0.7 in the control group EEG parameters and evoked potentials improved before clinical improvement; 13/25 of the patients showed improvement. Total follow-up was 3 months after DBS placement	severe brain injury DBS may be beneficial for PVS
Kanno 1989/effects of dorsal column stimulation (DCS) on reversibility of neuronal function—experience of treatment for vegetative states	Retrospective case series	$N = 23$, all in a vegetative state for a minimum of 3 months, <i>etiology</i> ten trauma, eight stroke, four hypoxic event, one tumor. “Most of the patients were young” without specific ages identified	Dorsal Column Stimulation (DCS), electrode was implanted midline at C2 under general anesthesia	Video recording of clinical condition EEG rCBF by SPECT CSF NE, DA, DOPAC, HVA, 5HT as measures of catecholamine metabolism	8/23 (34.7 %) individuals had good clinical improvement and seven improved to a level of being able to follow verbal orders	Potential value for dorsal column stimulation following severe brain injury
Lei 2015/right median nerve electrical stimulation for acute traumatic coma patients	Prospective randomized trial	$N = 437$ comatose patients after severe TBI, ages 6–65 years, initial GCS 8 at the RMNS group presentation, and remained 8 at 2 weeks	Participants enrolled 2 weeks after their injury and assigned to ($n = 221$) receiving electrical stimulation for 2 weeks or the control group ($n = 216$) treated by standard management. RMNS was for 8 h each day for 2 weeks	Glasgow coma score FIM score	After the 2-week treatment, RMNS patients had a more rapid increase of the mean GCS. Statistical significance not reached ($p = 0.0532$). 6-month post-injury a lower proportion of vegetative persons in the RMNS group than in the control group ($p = 0.0012$). FIM scores higher with RMNS ($p < 0.001$)	RMNS was tolerated without adverse complications and may promote recovery following brain injury when used in the early phase
Mitchell 1990/coma arousal procedure: a therapeutic intervention in the treatment of head injury	Case-control series	$N = 24$, 20 male and 4 female, severe head injury, ages 17–42 with mean 22.5 years, matched pairs by age, sex, type, and location of head injury, surgical intervention and Glasgow coma scale score at time of presentation	Treatment group had vigorous sensory stimulation administered by relative, initiated 2–12 days following injury. Visual, auditory, olfactory, tactile, and gustatory stimuli. Stimulation done 1–2 times a day	Duration of coma GCS	The total duration of coma was significantly shorter (22 versus 26.9 days) and coma lightened more rapidly in the treatment group	Potential value for multisensory stimulation following severe brain injury

Authors/Title	Study design	Study population/demographics	Intervention	Outcome measures	Results	Conclusions
Noda 2004/ therapeutic time window for musicokinetic therapy in a persistent vegetative state after severe brain damage	Case series	N = 26, PVS, ages 14–72 median 38.5 years, 18 male and 8 female. Etiology 12 head trauma, 9 subarachnoid hemorrhage, three other cerebrovascular accidents, two anoxic encephalopathy	MKT using vertical motions on a trampoline with live music performance for 30 min/ session, one time a week for 3 months	PVS score	25/26 patients had improvement in PVS score. Greater score improvements in participants with trauma or SAH than seen with other cerebrovascular accident or anoxic brain injury	Potential value for Musicokinetic therapy (MKT) following severe brain injury
Pierce 1990/the effectiveness of coma arousal intervention	Case series	N = 31 in coma or persistent vegetative state 2 weeks after severe closed head injury, 21 male and 10 female, age 6–75 with mean age of 24	Vigorous multisensory stimulation (auditory, vestibular, visual and cutaneous sensory systems) by a relative up to 8 h a day (average 6 h), 7 days a week for 2–32 weeks	Time to simple command following Glasgow coma scale 10–12-month post- injury	No significant improvements noted in the time to obey a simple command or in the Glasgow outcome scale	Coma arousal with vigorous multisensory stimulation did not improve outcome in patients with severe brain injury
Pistola 2013/ corticomotor facilitation in vegetative state: results of a pilot study	Cross-sectional survey	N = 6, PVS following brain injury for at least 3 months	Corticomotor facilitation induced by TMS. Consecutive MEPs were elicited under rest, execution, and observation to imitate	Changes in MEPs values from the abductor pollicis brevis muscle Improvement in scores on the coma recovery scale- revised	TMS may promote recovery of elementary motor activities in some patients in a vegetative state	TMS alone or with verbal instructions yielded no change; combination with imitation caused shorter latency, increased amplitude MEPs, with behavioral improvement in 4/6 patients
Sahni 2012/use of hyperbaric oxygen in traumatic brain injury: retrospective analysis of data of 20 patients treated at a tertiary care center	Retrospective case-matched series	N = 20 with TBI treated with HBOT. Age and severity matched patients with standard treatment as controls (n = 20)	Hyperbaric oxygen therapy of at least 30 sessions in addition to standard management	DRS GCS Rancho scale	Maximum DRS improvement in patients with scores of 22–24 (vegetative state), with more patients on HBOT improving than in controls Rancho scale improved to 3 in 60 % of HBOT versus 30 % of controls	Potential value for HBOT following traumatic brain injury
Seledtsov 2005/cell transplantation	Case-controlled, retrospective study	N = 38, patients with severe traumatic head injury, GCS 3–7, who,	Cells prepared from fetal nervous and hematopoietic	GCS score	Transplantation improved	Potential value for cell

Authors/Title	Study design	Study population/demographics	Intervention	Outcome measures	Results	Conclusions
therapy in reanimating severely head-injured patients		underwent cell transplantation, and 38 controls	tissues given via lumbar puncture to subarachnoid space		wakening and neurological status Favorable GOS outcomes in 33 (87 %) cell-grafted, 15 (39 %) control patients No serious complications noted	transplantation following traumatic brain injury
Wilson 1996/ vegetative state and responses to sensory stimulation: an analysis of 24 cases	Case series with meta-analysis.	N = 24, vegetative state following TBI. Age 12–50 years with mean 28.75 years	Multisensory stimulation	Behavior changes suggesting increased arousal	Multimodal stimulation produced greater changes than unimodal stimulation Personally salient stimuli in multimodal stimulation produced the greatest changes Age (older age at injury) and gender (female) showed effects on behavior change but time since injury did not	Potential value for multisensory stimulation with personally salient stimuli following traumatic brain injury
Wood 1992/ evaluating sensory regulation as a method to improve awareness in patients with altered states of consciousness: a pilot study	Case-matched controlled retrospective pilot study	N = 4 undergoing sensory regulated environment (experimental), age 12–33 and N = 4 sensory stimulation in an unregulated environment (control), Age 16–27	Sensory regulation model (reduced noise, breaks between nursing/therapy, sessions without stimulation)	Glasgow coma score Rancho score	Experimental group made greater progress with GCS compared to the control group Experimental group made greater gains with Rancho score compared to the control group	Patients in a vegetative state responded well to a sensory regulation procedure

3MT3-methoxytyramine, 5HTAA 5-Hydroxyindoleacetic acid, 5HT 5-hydroxytryptamine, ABS = agitated behavior scale, CRS-R coma recovery scale—revised, CSF-cerebrospinal fluid, CT cell transplantation, DA dopamine, DBP diastolic blood pressure, DBS deep brain stimulation, DCS dorsal column stimulation, DOPAC 3,4-dihydroxyphenylacetic acid, DRS disability rating scale, EEG electroencephalography, FIM functional independence measure, GCS Glasgow coma scale, HBOT hyperbaric oxygen therapy, HR heart rate, HVA homovanillic acid, ICU intensive care unit, MAP mean arterial pressure, MAS modified Ashworth scale, MCS minimally conscious state, MEPs motor-evoked potentials, MKT musicokinetic therapy, MVC motor vehicle collision, NDS non-directed stimulation, NE norepinephrine, O2 SAT oxygen saturation, PVS persistent vegetative state, Rancho scale Rancho levels of cognitive functioning scale, rCBF regional cerebral blood flow, RMNS right median nerve electrical stimulation, SAH subarachnoid hemorrhage, SBP systolic blood pressure, SDS specific-directed stimulation, SPECT single-photon emission-computed tomography, TBI traumatic brain injury, tDCS transcranial direct current stimulation, TMS transcranial magnetic stimulation, WNSSP western neurosensory stimulation profile