Rehabilitation Following TBI

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Introduction

Traumatic brain injury (TBI) can cause a wide variety of motor, cognitive, behavioral, emotional, and medical problems. Rehabilitation following TBI is, therefore, a complex endeavor requiring a team approach involving physicians, nurses, neuropsychologists, psychotherapists (e.g., psychologists, social workers, or mental health counselors), speech and language pathologists (SLPs), occupational therapists (OTs), physical therapists (PTs), vocational counselors, recreational therapists, and case managers. This entails the need for strong communication among team members and considerable flexibility on the part of the team. Therapists often have to take roles that may not be required in other settings. For instance, physical therapists will treat the physical mobility issues, including community navigation skills and safety. However, they have to be tuned into how cognitive dysfunction will affect mobility and how best to address it. They will also be confronted with the behavioral disorders that are prominent among people with TBI: disinhibited behavior, including aggression, but also apathy. OTs will work on activities of daily living (ADLs) and upper limb mobility, but will do so in the context of cognitive disability as well. Home and community skills, such as balancing a checkbook, meal preparation, and shopping, will take on greater importance in the rehabilitation of people with TBI because of the cognitive dimension. OTs, too, will have to treat behavioral disorders. SLPs will treat not only language, swallowing, and speech deficits among people with TBI but also cognitively based communication deficits. They will also treat problems with memory, attention, and executive skills and may overlap with OTs in the areas of home and community skills, such as scheduling and money management. Of course, SLPs will have to know how to manage behavioral issues as well. Nurses and the nurses' aides will have to deal with every dimension: medical, mobility, cognitive, and behavioral. Most TBI programs have neuropsychologists and/or behavioral psychologists who do neuropsychological assessments; guide the team with respect to cognitive, emotional, and behavioral treatments; and sometimes do counseling. The neuropsychologist has to apply his or her understanding of the cognitive and behavioral issues to pharmacology, mobility, ADLs, and home and community

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rehabilitation. Although important in all areas of rehabilitation, in rehabilitation following TBI, it is crucial that the physician listens to all team members, as well as family members. The physician is not going to learn all the details of what a patient is doing and saying with respect to emotional, behavioral, and cognitive status directly from the patient. The therapy and nursing staff, as well as family, will be the ones who observe the intricacies of the patient's inattention, disinhibition, and apathy and hear about the patient's despairing thoughts and so forth. At the same time, if the physician starts the patient on a medication for a cognitive, emotional, or behavioral issue, he or she will get a more complete perspective on the patient's response by hearing from other team members.

When it comes to treating physical issues, it is important that team members communicate their findings and concerns to one another. Disorders of muscle tone can change from moment to moment and differ with position. The therapist may see these changes manifested in different ways than will the physician. If the physician is going to intervene with medications or procedures, it is important that he or she understands the functional context in which the problem occurs. Again, the other team members' input will give the physician the information needed to make decisions about whether to try medications or whether or not they have been beneficial.

Medical problems, too, will affect the patient in every setting. It is important for the therapy staff to be aware of the medical status of the patient, which may change the person's physical, cognitive, and behavioral status. Therapy staff or family may be the first to see a change in a patient's status that will alert the physician to the possibility of medical issues or side effects of medications. Medical issues are covered in other chapters in this book.

Inpatient rehabilitation following TBI results in improved outcomes. Inpatient multidisciplinary rehabilitation beginning 4 weeks or less from the time of injury improved independence in mobility and ADLs in patients with severe TBI compared to a control group of inpatients in nonspecialty hospitals. Caregiver distress decreased more in the intervention group as well [1, 2]. Salazar and colleagues [3] did a randomized controlled trial (RCT) of inpatient cognitive rehabilitation vs. education, advice, and weekly telephone follow-up in a population of independently ambulating military personnel with TBI who had a Glasgow Coma Scale (GCS) score of 13 or less at the time of injury and a current Rancho Los Amigos Levels of Cognitive Function Scale (RLAS) score of 7. They found no difference in gainful employment or fitness to return to military duty nor in cognitive and behavioral/emotional performance between groups. However, a post hoc analysis found that among the more severely affected (loss of consciousness [LOC] greater than 1 h), the inpatient rehabilitation group had a better rate of return to duty [3]. The appropriateness of this high-functioning group for inpatient rehabilitation has been questioned [4]. RCTs have found that additional therapies [5] or the presence of an experienced brain injury professional on the rehabilitation team [2, 6] results in more rapid gains, but does not seem to change the ultimate outcome [2]. The vast majority of patients who attend inpatient rehabilitation programs following acute care are discharged to home. Older age, living alone before the injury, and lower admission FIM (Uniform Data System for Medical Rehabilitation, a division of UB Foundation Activities, Amherst, NY, USA) instrument scores in bladder management, bed-chair-wheelchair transfers, and comprehension are associated with discharge to skilled nursing facilities and other institutions [7]. Lower discharge FIM scores in bladder management, locomotion, and socialization are also associated with institutional discharge [8].

Controlled studies have also found post-inpatient residential, outpatient, and home rehabilitation to be effective for people with TBI. A single-blind RCT of community-based team rehabilitation for patients with severe TBI 3 months to 20 years after injury (mean 27 weeks) demonstrated improved mobility, ADLs, and participation-level skills (Brain Injury Community Rehabilitation Outcome [BICRO]-39 scales) in 40% of patients compared to 27% of the controls given only written information [2, 9]. In a single-blind RCT of a home-based multidisciplinary rehabilitation program for patients with severe

TBI, improved mobility and ADLs were seen, as well as participation-level outcomes on the BICRO-39 in the intervention group [2, 10]. An RCT comparing holistic, integrated cognitive, interpersonal, and functional outpatient rehabilitation with individual discipline-specific outpatient therapies for patients with TBI reported significantly greater gains in community functioning, quality of life, and self-efficacy for management of symptoms in the holistic rehabilitation condition [11]. A prospective cohort study comparing a residential rehabilitation program with a 3-month waiting list control group and 1-year follow-up found gains in independent living, societal participation, emotional well-being, and quality of life in the rehabilitation group of patients with chronic acquired brain injury (ABI) (67% TBI) and psychosocial problems affecting their ability to function in society [12]. A 3-year follow-up found the gains to be maintained [13]. Malec and Kean [14] analyzed a large database (N = 3087) from post-inpatient programs and found gains in the Mayo-Portland Adaptability Inventory (MPAI)-4 in residential and outpatient community-based rehabilitation compared with maintenance supported living programs. Participants were a mean of 587 days (SD = 1789 days) post-injury.

Motor Disorders

Definitions

There are several motor disorders commonly affecting people with TBI. Weakness is probably the most common disorder and can be addressed with strengthening exercises. This has not been studied in detail in people with TBI. Weakness is often seen with other motor disorders. These disorders are often seen together in various combinations, so it is best to start with definitions and descriptions.

Signs of ataxia include intention tremor and postural tremor. These are perhaps the most difficult of all motor disorders to treat. Although buspirone may have some modest effects on ataxia [15], there are no medications that have been shown to have clear clinically significant benefit. Weighted extremities can help at times, but the effect is small. Velcro wrist or ankle weights or ankle-foot orthoses with double metal uprights can be used. The only approach that is always worth trying is repetitive therapeutic exercise (e.g., reaching for a target or picking up a cup of water and bringing it to the mouth or, for the lower limbs, walking with as narrow a base as possible). Some patients will make slow gains with thousands of repetitions of the same activity. Others will be left frustrated by the lack of progress. Goals should be set that are achievable in order to minimize frustration.

Spasticity and rigidity are both disorders of muscle tone. Muscle tone is reflexive resistance to passive stretching of muscle. Spasticity is a manifestation of hyperactive stretch reflexes, one aspect of the upper motor neuron syndrome. It is characterized by a velocity-dependent increase in muscle tone (hypertonia) with a catch and release (including the specific "clasp knife" phenomenon), hyperactive deep tendon reflexes, and, at times, clonus. It is often seen with other aspects of the upper motor neuron syndrome: weakness, impaired timing, and poor coordination [16, 17]. It is important to treat spasticity in instances where it causes functional limitations; interferes with daily tasks, such as dressing, hygiene, or proper positioning in a wheelchair; or generates a significant degree of pain. Spasticity is not always detrimental and can sometimes provide functional benefit. In some cases, lower extremity spasticity may not impact mobility outcomes [18], and increased muscle tone in the hip and knee extensors may allow a person to bear weight on an otherwise weak extremity. Spasticity of the elbow flexors can make it possible for someone to carry a purse or shopping bag on the forearm. Increased tone in the finger flexors can allow a person to hold objects in the hand.

Rigidity is another form of hypertonia. In this case, the increase in muscle tone is not velocity dependent, and it is consistent throughout the available range of motion [16, 19]. Parkinsonian rigidity with cogwheeling can occur after TBI. In addition, gegenhalten or paratonia, in which there is a feeling of voluntary resistance [20, 21], can be seen as well.

Dystonia is also quite common. Dystonia occurs when involuntary muscle contractions result in intermittent or persistent posturing [16, 19, 22, 23]. Dystonia is not necessarily a hypertonia; that is, it may or may not be elicited by a muscle stretch. It can be seen spontaneously or can be elicited by a sensory stimulus, such as touch, perturbation, or even a loud noise. Technically, decerebrate and decorticate rigidity are dystonias. Spasticity can result in dystonic posturing. There is probably more than one neurophysiologic etiology.

Although more commonly seen in spinal cord disorders, involuntary flexor or extensor spasms of the limbs can be seen after TBI. These are sudden jerking movements that are manifestations of hyperactive cutaneous or soft tissue reflexes. Synergies and, less commonly, postural reflexes can be seen after TBI as well. These are obligate patterns of movement initiated by active (synergies and postural reflexes) or passive (postural reflexes) motion of a limb or, in the case of postural reflexes, the head and neck or trunk. The individual is unable to move joints in isolation [16, 24].

Treatment

The mainstay of treatment of the upper motor neuron syndrome for all of these entities is therapeutic exercise and functional training done by physical and occupational therapists, including sustained stretching of muscles and soft tissues. Electromyographic (EMG) biofeedback can be helpful to facilitate isolation of the muscles that are most problematic, though the literature on its efficacy is limited [25, 26]. Although thus far the best evidence for its efficacy has been in subjects with stroke, constraint-induced movement therapy (CIMT) [27] or a modification of the full therapy [28, 29] can be done for the hemiplegic individual with TBI who is capable of complying with the rigorous schedule [30]. It is most frequently used to facilitate movement of a partially impaired upper limb. In full CIMT, the patient receives therapy for the more impaired limb 6 h a day, combining repetitive task practice with adaptive task practice. The latter involves practice of components of the task and eventually the entire sequence, with a gradual increase in task difficulty. The stronger limb is restrained with a mitt or other devices for 90% of waking hours, forcing the patient to use the partially impaired extremity. The patient keeps a log of his/her activities as a check on compliance and to reinforce the behaviors. It has been successful in the subacute and chronic settings where it has been shown to improve upper limb use following stroke [27, 31]. However, limb restraint in the acute rehabilitation setting has been unsuccessful and even detrimental with a more intensive therapy group [32]. CIMT is based on the hypothesis that people with hemiplegia make limited gains in the use of the impaired upper limb because of "learned disuse." This theory suggests that in the early days of rehabilitation, people with hemiparesis who do not make rapid gains will limit the use of the impaired extremity and instead emphasize compensation using the stronger extremity because of the frustration and lack of positive reinforcement received from limited success. Thus, the full potential for recovery is not reached [33].

The initial approach to problems with spasticity includes treating provocative nociceptive influences, in particular, skin, bladder, and bowel problems. This decreases the noxious input into the central nervous system (CNS) that facilitates excitation of motor neurons [16, 20]. Sustained stretch through range of motion exercises is also key and generally needs to be done at least daily if there is a significant amount of spasticity. Positioning is also crucial for limiting spasticity. For instance, if, when sitting in a wheelchair, a person is tending to slide out due to hip and knee extensor tone, a tilt-in-space wheelchair will take advantage of gravity to hold the hips in flexion. A seatbelt across the pelvis will help to keep the hips at 90 degrees. If the toes are held down with toe loops, the knees will remain flexed. Maintaining this position will stretch the hip and knee extensors as well as the ankle plantar flexors, and the spasticity will decrease [34].

There are also a number of physical modalities that physical and occupational therapists use

to treat spasticity that tend to work in the short term and can be used before stretching or other therapeutic exercises. Warmth can decrease muscle tone. Cold generally increases spasticity in the short run, but after 15 or 20 min, it will decrease the tone [35]. Ultrasound is a deep heating method. If the elastic portions of the tendon and muscle are warmed, they become more flexible, and then more stretch can take place before the muscle spindle gets stretched. Electrical stimulation can be used, both in the antagonist and the agonist muscles. In the antagonist muscle, reciprocal inhibition is leveraged to inhibit the muscle tone in the agonist muscle. In the targeted agonist muscle group, electrical stimulation over a period of time can deplete acetylcholine from the neuromuscular junction, thus fatiguing the spastic muscle [35]. However, small studies investigating the coupling of electrical stimulation to splinting do not appear to demonstrate added benefit compared to stretching and splinting alone [36]. Low-frequency generalized vibration can also be used to decrease spasticity [37].

Casting and orthotics can decrease muscle tone, though casting tends to be more effective [35, 38, 39]. If well applied, the soft tissues are held in a position for a sustained period of time, thus reducing muscle tone. However, a cast or orthotic that does not hold a joint well and allows for some movement will often provoke an increase in tone by acting as a noxious stimulus to the skin.

Medications can be helpful, though are used less frequently in people with brain injury than with spinal cord injury because many of them have deleterious cognitive side effects. Diazepam and other benzodiazepines cause sedation, as well as attention and memory problems that may persist following withdrawal [40, 41]. They are generally to be avoided except in situations in which the hypertonia, dystonia, or muscle spasms are so severe as to be painful or otherwise disruptive, thus becoming a major distraction to the patient, and in which other approaches have either failed or are relatively contraindicated. They are not FDA approved for this use ("off-label"). Baclofen can be useful for treating spasticity and muscle spasms but has been found to impair memory in animal experiments [42, 43]. There is little evidence for its efficacy in people with spasticity caused by cerebral lesions [35], although anecdotally, individual clinicians have found it helpful at times. Cyproheptadine has been used to treat spasticity, but studies in people with spasticity resulting from cerebral lesions are extremely limited. Its sedating effect can be a major drawback [35]. Clonidine was used more frequently in the past ("off-label") but has largely been replaced by tizanidine, which is also a central alpha-2 agonist that decreases spasticity, but with less effect on blood pressure. However, side effects, in particular sedation, often limit its use. Because of data suggesting that clonidine can inhibit recovery from CNS lesions, tizanidine is suspect as well [35]. Tizanidine can also cause elevated liver function tests [35]. As an "off-label" use, gabapentin has been shown to be effective for treating spasticity in persons with multiple sclerosis at doses of about 2700 mg a day [44], though individual dosing varies. Gabapentin can be sedating, but if titrated slowly, many patients accommodate to this effect. It is otherwise generally free of adverse cognitive effects [44–46]. Dantrolene sodium is generally thought to be without deleterious cognitive effects, though studies in animals have shown an adverse effect on memory [47, 48]. Whereas the drugs previously mentioned work in the CNS at the reflex level, dantrolene works at the muscle itself by inhibiting the release of calcium from the sarcoplasmic reticulum. Hepatotoxicity is a serious potential problem, so liver function tests must be followed. However, efficacy appears to be optimal at doses of 200 mg daily or less, and at that dose the risk of hepatotoxicity is small. Dantrolene does tend to cause weakness in the non-spastic muscles [35]. Because it acts peripherally, any muscle can be affected by it. Although generally not a problem if the muscle is unused or is strong, in areas where the person is weak, dantrolene may tip them over the edge into weakness that affects function, including muscles involved in swallowing and speech. Compliance with oral anti-spasticity agents has been found to be relatively poor in the TBI population, particularly among younger individuals [49].

When cogwheel rigidity is present, the same dopaminergic agents that are used in Parkinson's disease can be tried ("off-label"), although this needs further study. Dystonia is very difficult to treat, and in patients with TBI, the pharmacologic approaches are "off-label." Anticholinergic agents can be used, though they are generally of limited benefit [50]. They can adversely affect memory and attention [51, 52]. Benzodiazepines can be very effective, but as noted above, they can cause sedation and cognitive impairment [40, 41].

Chemical denervation using botulinum toxin, phenol, or even alcohol will often provide a better risk-to-benefit ratio because of the lack of cognitive side effects. This is particularly the case when hypertonia or dystonia is focal rather than generalized or in situations in which the need for intervention is limited to a small number of areas. Chemical neurolysis with phenol destroys axons, but weakness is not a common complication if used discretely. There is a very variable duration of action, from weeks to years. It often lasts longer than 6 months, which is in some ways an advantage and in other ways a disadvantage over botulinum toxin. It is most useful when the patient cannot or does not want to return frequently for injections, when the limit for the quantity of botulinum toxin has been reached and there are still areas in need of treatment, or when botulinum toxin is not effective. It can also be used as an adjunct to botulinum toxin. When only motor branches are blocked, then the common side effects are transient pain and occasionally swelling at the injection site, depending on how much is used and which muscles are injected. If mixed sensorimotor blocks are done, some patients (10–32%) will get dysesthesias in the sensory distribution of the nerve. This is usually a mild "pins and needles" sensation that lasts for 2 or 3 weeks and then resolves. Occasionally, these painful sensations need treatment with transcutaneous electrical nerve stimulation, a tricyclic antidepressant ("off-label"), or other medications until they have run their course. Rarely dysesthesias continue for longer periods of time. In such cases, reinjection with phenol at the same site will usually resolve the pain. The best approach to this issue is to prevent the problem entirely by doing motor branch blocks or injecting peripheral nerves that are largely motor, such as the thoracodorsal or obturator nerves. Usually, a motor branch block is sufficient to reduce spasticity, but mixed sensorimotor blocks are at times necessary to get a better result. Goals of treatment should be clear before injections are done [21, 53]. The use of phenol to treat hypertonia or dystonia is not FDA approved.

Botulinum toxin inhibits release of acetylcholine at the neuromuscular junction. There are several serotypes, but the only ones that are commercially available are botulinum toxins A and B. Within each serotype, there are preparations that differ according to the company that produced the toxin. The duration of effect (generally 2–6 months) is usually shorter than with a phenol block. This makes it a better choice when there is a concern that the procedure might adversely affect a person's function. There is a limit to how much botulinum toxin can be used in any given therapeutic period (approximately 3 months). If there are several muscle groups to cover, especially when bilateral procedures are necessary, it may not be possible to treat them all with botulinum toxin. There is a limit to how much phenol can be injected in a given day, but over a period of a few weeks, more can be used [53]. Botulinum toxin is relatively free of side effects and complications, although dysphagia and respiratory insufficiency have been reported even with therapeutic doses [54, 55]. Dysphagia is more common when cervical muscles are injected. Rates of dysphagia and dry mouth may vary among different preparations/brands [56]. There can be diffusion of toxin to local muscles that are not targeted. As with phenol, it is important to clarify the specific goals of treatment prior to the procedure [53]. In RCTs, botulinum toxin A has been demonstrated to reduce upper limb spasticity in individuals with stroke and brain injury [57, 58] and to improve muscle tone and performance on specific simple functional tasks, such as putting an arm through a sleeve, cleaning the palm of the hand, or cutting the fingernails [54]. Improvement in lower limb spasticity can also be achieved with injections of botulinum

toxin A in individuals with stroke and brain injury [58, 59]. RimabotulinumtoxinB has also been demonstrated to improve upper limb spasticity after TBI or stroke [60]. When used for cervical dystonia, however, there may be a higher incidence of dysphagia and dry mouth with the use of botulinum toxin B compared to botulinum toxin A [61]. The botulinum toxin preparations available in the USA are FDA approved for certain dystonias in adults and detrusor or bladder overactivity. Onabotulinum toxin A is approved for spasticity of the thumb, fingers, wrist, elbow flexors, toes, and ankle plantar flexors in adults; but it is commonly used in other muscles "off-label."

In an open study, selective tibial motor neurotomy was shown to decrease spasticity and improve dorsiflexion strength and gait on a long-term basis (at least 2 years) in patients with hemiplegia. Plantar flexion strength eventually returned to baseline due to collateral sprouting, while decreased spasticity is maintained due to the inability of IA afferents to reconnect at the spinal cord level [62].

Local anesthetic nerve blocks can be used as a "test run" before using botulinum toxin, phenol, or neurotomy in order to ascertain whether or not reducing tone in a muscle or group of muscles will provide any benefit or adversely affect function. Local anesthetic blocks can be helpful when there is a question of whether the inability to move a joint beyond a certain range of motion is due to severe hypertonia or contracture. The local anesthetic trial is, of course, no guarantee, as it is not likely to be exactly comparable to the other procedures [21, 53].

Baclofen pumps can also reduce spastic hypertonia in people with TBI [63, 64] by delivering small quantities of baclofen directly to the intrathecal space, thus avoiding the systemic effects of baclofen. A potentially life-threatening withdrawal syndrome with high fever, altered mental status, and muscular rigidity can occur if the baclofen is suddenly cut off, either because the reservoir is depleted or there is a malfunction in the pump or catheter [65]. Regular visits for refills must be scheduled. Today's pumps have alarms that alert the patient that the pump is in danger of becoming empty.

There are also orthopedic procedures, such as muscle and tendon lengthenings and transfers, which help to decrease muscle tone. Lengthenings are done in the context of treating contractures. A small study in individuals with stroke and TBI demonstrated tendon fractional lengthening of the pectoralis major, latissimus dorsi, and teres major improved both passive and active shoulder flexion, abduction, and external rotation and reduced pain [66]. Tendon transfers are usually done for the purpose of improving function. The split lateral anterior tibialis tendon transfer for the treatment of ankle-foot inversion is an example. The tibialis anterior tendon is split at its insertion, and half of it is taken from the medial side of the foot and implanted on the lateral foot, such that it is now balancing the inversion with an eversion pull, thereby dorsiflexing the ankle in a neutral position [67, 68]. When ankle plantar flexion contracture accompanies inversion, the Achilles tendon is lengthened as well. In order to preserve the ankle plantar flexion strength, the flexor digitorum longus and flexor hallucis longus can be transferred to the calcaneus [67]. Surgeons and referring clinicians must beware of the possibility of overcorrection resulting in the dominance of antagonist muscles, both with lengthening and transfers [68].

Persistent hypertonia and/or immobility can result in contractures. The main approaches to the prevention of contractures are range of motion exercises and proper positioning. Other approaches to spasticity and dystonia referred to above may be necessary as well. If contractures have developed, serial casting is an excellent way of reducing them. A cast is placed with the limb in close to the full achievable range of motion and left on for 3–7 days. Muscle tone will be reduced. When the cast is removed, there will often be more passive range of motion available. Another cast is placed that takes advantage of these additional gains. This process continues until no additional range of motion is achieved [37, 69]. However, the reduction of contractures in response to serial casting in patients with TBI may be transient [70, 71]. Botulinum toxin injections to reduce spasticity prior to casting have been found to help sustain the results in children

with cerebral palsy [72, 73]. Long-term studies of botulinum toxin injections, combined with serial casting, in adults or children with TBI need to be done.

When serial casting is not feasible, adjustable spring-loaded dynamic orthotics can be used to place maximum tolerable tension on the contracted soft tissues, with gradual changes in joint angle and tension being made overtime [74, 75]. These orthotics have the advantage that the skin can more easily be observed for pressure ulcers, but they are not as effective as casting, partly because the patient can remove them. When these approaches fail, surgical lengthenings may be indicated.

Heterotopic ossification (HO) in the large joints is not uncommon among people with severe TBI. It is associated with longer duration of coma, longer period of mechanical ventilation, surgically treated fractures of the extremities, and the development of autonomic dysregulation [76]. HO can be extremely painful during range of motion exercises. Patients may be very resistant to range of motion exercises while HO is forming. HO often progresses to complete ankylosis of joints. It can entrap peripheral nerves with resultant neuropathy. Disodium etidronate and nonsteroidal anti-inflammatory drugs (NSAIDs) have both been used for prevention, although the evidence for their beneficial effect is largely from studies in other patient populations, such as spinal cord injury and hip surgery [77, 78]. There is, in particular, an unanswered question as to whether the preventive effect of etidronate is only short term [79]. Although disodium etidronate is generally well tolerated with serious side effects being rare, NSAIDs can cause gastric and duodenal ulcers and, less commonly, adverse cardiac events [77]. Some physicians use etidronate or NSAIDs prophylactically in people who have been in coma, vegetative state, or minimally conscious state for significant periods of time (the populations at increased risk of developing HO) [80]. Other clinicians will wait until there are symptoms. Usually HO begins with an inflammatory response resulting in a painful, warm, swollen, and erythematous area. It can be mistaken for a deep vein thrombosis (DVT), cellulitis, or deeper infection. Alkaline phosphatase and creatine phosphokinase will generally be elevated. At that point, it will not show up on an X-ray, but a triple-phase bone scan will be positive. It can take 3–4 weeks before it becomes calcified sufficiently to be seen on an X-ray. Some physicians get bone scans when the inflammatory response is seen and DVT is ruled out; and if there is uptake on the bone scan in that area, then they will start disodium etidronate or an NSAID or administer radiation, another treatment that has been effective in patients with SCI or following hip surgery. Once formed, the HO often restricts range of motion or fuses a joint. A retrospective review of surgical excision of shoulder HO in a small cohort of patients with TBI demonstrated significant improvements in all planes of shoulder motion, improved functional status, and increased independence with feeding, grooming, and toiletry [81]. There is no evidence that waiting more than a year after injury to do a surgical excision is associated with a decreased chance of recurrence [82]. Disodium etidronate, NSAIDs, and/or radiation can be effective for the prevention of recurrence after surgery [77, 78, 83]. There are also case studies suggesting the use of extracorporeal shock wave therapy as a therapeutic invention to improve range of motion by way of reducing pain from HO [84, 85], but more robust studies are needed to clearly demonstrate its effectiveness.

Dysphagia

Dysphagia is a common disorder following TBI. Dysphagia is dependent on the status of the oral-motor musculature as evaluated by modified barium swallow (MBS) [86, 87], but also on the patient's cognitive status [88]. Lack of basic orientation and the inability to follow commands are predictive of aspiration [89]. Even among patients with higher levels of cognitive function, poor self-monitoring and impulse control can affect swallowing ability due to difficulty monitoring bolus size and speed of swallowing. Other predictors of dysphagia following TBI include RLAS score, GCS score on admission, presence

of a tracheostomy, and longer ventilation time [86, 88, 90]. It is not necessary to be feeding orally to develop pneumonia in the early stages of recovery; and, in fact, one study found that 81% of people with TBI who developed pneumonia were not receiving anything by mouth [90]. One can aspirate secretions and refluxed or regurgitated stomach contents; and respiratory insufficiency, inadequate or absent cough, and lack of mobility can cause or contribute to pneumonia as well. One study found that 41% of patients with TBI who aspirated were found to do so silently, i.e., without coughing [86]. Disability rating scale score, RLAS score, and oral-motor disorders on MBS are predictors of aspiration at 1 year after TBI [86, 87]. The MBS is considered the standard for evaluating swallowing. Even individuals with tracheostomy can undergo MBS and start treatment for swallowing [91]. Fiber-optic endoscopic evaluation of swallowing (FEES) can also be used for a better view of the pharynx [92].

The management of dysphagia involves trials of food and liquid consistencies as determined by MBS. Head and neck postural techniques and exercises, both tailored to the individual aspect of swallowing that is disordered, can improve performance [92]. In an RCT, 55% of patients with TBI and stroke with neurogenic dysphagia avoided aspiration with a chin-down posture as demonstrated by video fluoroscopy. However, of the 51% of study participants who were silent aspirators, 48% continued to demonstrate aspiration despite the chin-down posture [93]. The use of neuromuscular electrical stimulation in combination with conventional swallowing therapy may be an effective intervention to accelerate improvement in swallowing function as demonstrated in a small RCT of 20 participants (14 stroke and 6 severe TBI) with neurological oropharyngeal dysphagia [94].

Cognitive Disorders

Cognitive Rehabilitation

Cognitive impairment will usually improve during the first or second year following TBI and sometimes up to 5 or 10 years post-injury [95]. Disturbances in the sleep-wake cycle are common after TBI, and sleep architecture and quantity and quality of sleep are associated with functional recovery [96]. Poor nocturnal sleep and daytime sleepiness in individuals with TBI have been correlated with impaired performance in cognitive domains such as attention, memory, and processing speed [96–100]. There are also interactions between sleep-wake disturbances and post-TBI pain, depression, and anxiety [101–103]. Pharmacologic interventions for sleep-wake disturbance for individuals who have sustained a TBI are currently under active investigation, and so far results have been varied (see Chap. 7). There is preliminary evidence to suggest that individualized treatment of sleep-wake disturbance using a combination of sleep hygiene strategies and pharmacologic interventions may reduce the severity of insomnia and improve language and processing, but such studies have been small and uncontrolled [104].

There are several aspects of cognition for which there is evidence for the benefit of therapeutic interventions. Processing speed, reaction time, attention, and response inhibition are commonly impaired following TBI [105]. A meta-analysis of 12 RCTs (237 individuals with stroke, 146 individuals with TBI, and 201 individuals with malignancy impacting the CNS) on the use of cognitive interventions for attention rehabilitation found short-term improvements in divided attention among individuals with stroke, but no significant improvements in sustained or selective attention or inhibition in individuals with TBI [106]. The duration of cognitive interventions ranged from 20 min to 7.5 h per week. However, of the four studies that reported long-term outcomes (follow-up of 2–12 months), there were no sustained effects from the interventions on selective attention, sustained attention, alternating attention, or inhibition in either the stroke or TBI populations [107–110].

Overall, memory impairment following TBI will demonstrate some degree of spontaneous improvement overtime, and cognitive rehabilitation strategies for memory can serve as effective treatment adjuncts [111]. The international

cognitive (INCOG) expert panel guidelines recommend the use of both internal and external compensatory strategies to improve memory [112]. For the treatment of memory disorders, there is some evidence for the benefit of teaching semantic strategies to people with TBI [113, 114]. This includes semantic association, semantic clustering, and semantic elaboration. Training in visualization and visual imagery techniques can be beneficial for people with mild memory problems [115, 116]. Preliminary evidence suggests that following severe TBI, retrieval practice, whereby individuals are quizzed on newly learned information, improves delayed recall after both short (30 min) and long delays (1 week) [117]. Working memory capacity is associated with effective learning ability after TBI, and further study is warranted [118]. External aids such as notebooks and appointment books can be quite helpful and are recommended [119–122]. For those who can learn their use, even in a limited fashion, tablet computers or "smart" mobile phones are often more useful than notebooks [123–127]. These can be programmed with reminder alarms and, therefore, do not rely on prospective memory as do appointment books. They may have to be programmed by somebody else if the person with TBI does not have the requisite skills, and some people with TBI need others to remind them to use the device [123]. Pagers are another external compensatory aid that have been found to be successful [128, 129]. There is evidence that therapy focused on metacognitive strategies and problem-solving skills may be effective in improving post-TBI executive function [130–133].

The effectiveness of therapies to improve hemi-inattention and aphasia has been largely demonstrated in subjects with stroke. It is not unreasonable to tentatively extrapolate to people with TBI until the evidence is available with this population. Spatial neglect, often, but not always, of the left side, can be decreased with consistent cueing to scan to the neglected side [120, 134]. Aphasia has been treated with functional language stimulation, cueing, and semantic analysis in people with stroke. The evidence suggests that such training is effective, but studies are not yet definitive [121, 135, 136]. There is limited evidence for the effectiveness of constraint-induced language therapy (CILT) in the chronic phase after stroke [135, 137–139]. In CILT, the person being trained is not allowed to use gestures or to write and is forced to communicate during a simple card game, for instance. A screen can be put up so that gestures cannot be seen. The person being trained has to initially have some language function, such as the ability to say the number on a card. One study demonstrated a positive effect of CILT and the NMDA receptor antagonist memantine used separately for the treatment of aphasia and a greater effect when used in combination [139]. There is limited evidence for the benefit of dextroamphetamine for the treatment of aphasia in the context of speech therapy [140].

There is also evidence for the efficacy of holistic cognitive rehabilitation programs in which cognitive, emotional, motivational, and social functions are addressed in a single program. Gains have been seen in employment and in community integration skills [141]. The use of telehealth services to administer cognitive therapy interventions has been demonstrated to increase treatment adherence in individuals with mild traumatic brain injury (mTBI) [142] and may be a promising means of reducing treatment barriers in the TBI population.

When a patient has problems with alertness, initiation, and/or attention, medical factors may need to be treated. Infection, electrolyte imbalance, and hydrocephalus can result in decreased arousal, attention, and initiation. Endocrine dysfunction is common and is addressed in Chap. 11. In one study of patients with disorders of consciousness secondary to TBI, more than 80% of 184 patients experienced at least one medical complication during inpatient rehabilitation [143]. Insomnia and other sleep disorders are also frequently seen after TBI [144] and are further addressed in Chap. 7. A prospective longitudinal study found that 67% of patients with TBI have persistent sleep-wake disturbances even 3 years post-injury [145]. Poor sleep, vitamin D deficiency, and anxiety are also commonly associated with chronic fatigue after TBI [146]. Conversely, fatigue also predicts anxiety, depression, and daytime sleepiness [147] and contributes to self-reported disability after TBI

[148]. There is evidence that treatment with high-intensity blue light therapy may help to alleviate fatigue and daytime sleepiness in patients with TBI [149]. Seizures can result in postictal lethargy and is also addressed in Chap. 10.

Pharmacological Treatment of Cognitive Disorders

Pharmacological approaches can be useful, particularly for treating arousal, attention, initiation, and other aspects of executive skills. The first pharmacologic intervention to consider is withdrawing offending agents, such as phenobarbital [45, 46, 150], phenytoin [46, 150, 151], carbamazepine [46, 151, 152], topiramate [45, 46, 153–159], zonisamide [46], pregabalin [46, 160], baclofen [42, 43], tizanidine [35], benzodiazepines [161], tricyclic antidepressants [162], opiates [163], and antipsychotics (especially the typical antipsychotics, such as haloperidol, chlorpromazine, and thiothixene) [162]. Among the anticonvulsants, levetiracetam [152, 159], gabapentin [46], tiagabine [46], vigabatrin [46], and lamotrigine [46] are relatively free of adverse cognitive effects, although sedation can be an issue with levetiracetam [150] and gabapentin. Studies on valproic acid [46, 164] and oxcarbazepine [46] are mixed with respect to their effect on cognition.

The benefit that a medication is providing must be weighed against the probability that it is causing cognitive impairment. Individual responses to medications vary considerably, so any change seen or not seen when the patient started the medication is important in determining whether it is causing adverse effects.

Insomnia is often a contributor to daytime sleepiness and cognitive impairment. When simple sleep hygiene approaches are not working, medications may be helpful. However, for the long term, if the patient is capable of participating effectively, cognitive behavioral therapy (CBT) is usually more beneficial than medications [165]. See Chap. 7 for further discussion of sleep disorders.

When other causes of attention, arousal, or initiation problems have been addressed to whatever extent possible, stimulants or stimulant-like drugs can be useful. The use of all medications discussed here is "off-label." This includes methylphenidate, amphetamines, modafinil, atomoxetine, dopaminergic drugs, NMDA receptor antagonists such as amantadine and memantine, and cholinesterase inhibitors. Methylphenidate has the best evidence for effectiveness in treating attention following TBI. RCTs have shown gains in on-task behavior and speed of processing, as well as improvement in fatigue, with administration of methylphenidate [166–170]. Methylphenidate comes in both immediate-release and long-acting formulations (see Table 1) [171]. Amphetamines have a similar mechanism of action, but have not been as well studied for the treatment of attention, initiation, or arousal deficits in people with brain injury. Lisdexamfetamine dimesylate, a prodrug

Table 1 Some long-acting formulations of methylphenidate

Drug taken once daily	Mechanism	Peaks (hours)[a]	Duration of action (hours)[a]
Metadate CD ER Capsules (UCB)	Beaded IR and ER MP, double-pulse release	1.5, 4.5	8–12
Ritalin LA (Novartis)	Beaded MP, double-pulse release, IR/DR	1–3, 5–7	
Concerta ER Tablets (Janssen)	Drug overcoat dissolves; then two internal layers gradually release drug	1–2, 6–8	10–12
Daytrana transdermal patch (Shire)	Multipolymeric adhesive – transdermal absorption	8, 10[b]	11.5[b]
Focalin XR (Novartis) (dexmethylphenidate)	Beaded MP, double-pulse release, second release at 4 h, IR/DR	1.5, 6.5	8–12

Data from: Refs. [340–346]

MP methylphenidate, *IR* immediate release, *ER* extended release, *DR* delayed release

[a]Most studies have been done in children

[b]Assuming 9-hour wearing time, peaks at 10 hours on first application, 8 h after multiple applications; includes 2-hour delay until MP appears in plasma

of dextroamphetamine, has been shown in a small RCT to improve measures of sustained attention, working memory, response speed, and some areas of executive function in participants with moderate to severe TBI at least 6 months prior. It also resulted in gains in more persistent difficulties with focused or sustained attention [172].

Amantadine can be effective for hastening, and perhaps improving, the responsiveness of individuals in a minimally conscious state during the first few months after injury [173, 174]. There is more limited evidence for an effect of amantadine on the outcome of inpatient rehabilitation [169, 175]. Although modafinil did not bring about improvement in fatigue and alertness following TBI in one small RCT [176], in another RCT, sleepiness but not fatigue improved [177]. Atomoxetine, a selective norepinephrine reuptake inhibitor, did not result in significant improvement on measures of attention in participants with moderate to severe TBI [178].

There is some evidence that acetylcholinesterase inhibitors can have a positive effect on sustained attention and anterograde memory in people with TBI [140, 169, 179, 180]. A study of rivastigmine in persons with TBI showed no benefit for the group as a whole, but positive results for visual processing speed latency and memory among those with moderate to severe injury in a secondary analysis [181]. Bromocriptine was shown to help dual-task attention in an early study [182], but this result was not replicated by Whyte and coauthors [183]. In the latter study, other aspects of attention also did not improve with bromocriptine. Protriptyline is a stimulating antidepressant that can be activating [184] but has not been well studied.

Behavioral and Emotional Disorders

Treating behavioral and emotional disorders requires an evaluation of the underlying contributing factors. Medical conditions such as electrolyte disturbance, endocrine disorders, infection, hydrocephalus, epilepsy, and others can cause behavioral changes. The loss of control that comes with being physically or cognitively disabled often results in depression and anxiety. Preinjury psychiatric issues often continue to play a role after a TBI. Staff, family, or friends may inadvertently reinforce aggressive and disruptive behaviors by paying undue attention to them. Antecedents to aggression must be evaluated to determine the triggers to such behavior.

Differential Diagnosis of Behavioral and Emotional Disorders

There are a number of behavioral disorders that are often seen after TBI. Sabaz and colleagues [185] reported an overall 54% prevalence rate of challenging behaviors. Disinhibition, aggression, and emotional dyscontrol are extremely common [186], usually as a result of frontal lobe lesions. Apathy is common [187], as are depression [188, 189] and anxiety [189, 190], often as a reaction to the disability once the person develops enough awareness. Posttraumatic stress disorder (PTSD) following TBI can also be seen, even among those with moderate to severe injury, especially in military populations. See Chaps. 13 and 15. Up to 66% of cases occur with delayed onset, peaking between 6 and 12 months post-injury [191]. PTSD is associated with shorter duration of posttraumatic amnesia (PTA), other concurrent psychiatric disorders, and lower functional and quality of life outcome scores following TBI [192]. Psychotic behaviors resulting from TBI are unusual, but do occur. New onset of mania is seen rarely.

Clinicians must be careful not to mistake the influences of cognitive and perceptual deficits for psychiatric syndromes. For instance, reduplicative phenomena caused by frontal dysfunction often include the belief that certain people are imposters. However, this can easily be mistaken for delusional thinking as seen in more classical psychiatric settings. Memory disorders can cause what appear to be hallucinations or delusions. A person with a severe memory disorder may, for instance, believe that someone important to them who has died is actually alive because he or she has no memory of the person's death, particularly if it occurred shortly before

the injury. Visual-perceptual impairment, especially in the context of executive dysfunction, can result in hallucinatory-like experiences. There can be a fine line between these sorts of behaviors and manifestations of actual psychosis. This is an important consideration because it may involve a decision about whether or not to use antipsychotic medication. There are no studies that address this issue, so the clinician has to use his or her best judgment. One consideration is whether or not there is significant emotion, in particular, fear, surrounding a belief. For example, if the person with TBI fears that they will be hurt by someone or something that they see or believe to exist, one would be more apt to treat it as a psychotic behavior than if the person is unconcerned. Other combinations of cognitive, behavioral, and perceptual problems can mimic psychiatric syndromes. Neurologically based apathy can mimic depression, except that the withdrawn, apathetic patient will not feel sad or be tearful [193].

Nursing and therapy staff or other caregivers will often be in the best position to provide information to physicians, psychologists, and social workers that may provide clues to the etiology of behaviors. They will often be the ones to hear the despairing words of a depressed patient, to observe that a patient does not initiate and shows little affect, to see the circumstances under which a person becomes aggressive, or to see whether fearfulness is associated with hallucinatory or delusional-like behaviors. They can see the degree to which a behavior is interfering with rehabilitation or causing disruption to the patient or to others' lives. Of course, this does not mean that the clinician should rely entirely upon others to evaluate behavior. Interviewing even very impaired patients can turn up clues that aid in diagnosis, and observing them in therapies or on the nursing unit can also be revealing.

Treatment of Mood and Anxiety Disorders

Some people with depression and/or anxiety following TBI can benefit from individual counseling despite some cognitive impairment [194]. Cognitive behavior therapy has been found to be helpful in treating distress following acquired brain injury [195]. However, problems with executive function, attention, and memory can be limiting factors. CBT directed at improving depression or anxiety has demonstrated some success in the TBI population [196, 197] and may be more effective in combination with motivational interviewing [198]. However, in one study, CBT had no significant effect on suicidal ideation [199]. An RCT also demonstrated no differences in efficacy between CBT and supportive psychotherapy for depression following TBI [188]. Group treatments can sometimes be helpful as well. A periodic telephone call inquiring about problems, providing needed information, and facilitating problem-solving has been found to be preventive of future depression and also to treat preexisting depression [200].

Medications can be used when depressive symptoms and/or anxiety interferes with quality of life and/or rehabilitation over a sustained period of time. Depression is best treated with low- or non-sedating antidepressants – the selective serotonin reuptake inhibitors (SSRIs) and SNRIs [169]. In a systematic review and meta-analysis, pharmacologic treatment of depression after TBI was found to be associated with significant reductions in depressive symptoms [201]. However, there was no difference in preventing a relapse of depression following TBI by continuing therapy with citalopram, a selective serotonin reuptake inhibitor, compared with placebo [202]. Antidepressants should be used cautiously, especially in the elderly, as SSRIs (and tricyclic antidepressants) have been associated with increased mortality and hemorrhagic stroke [203, 204]. This fact, however, must be weighed against quality of life issues and the known risk of cardiovascular disease and suicide in untreated depression [204]. Anxiety can also be treated with these medications. Benzodiazepines are best avoided when possible due to their adverse effect on alertness, attention, and memory, though occasionally the trade-off can be in favor of their use since anxiety itself can affect cognition. Buspirone is unlikely to cause cognitive side effects [205].

Treatment of Behavioral Disorders

Treating behavioral issues following TBI requires understanding and addressing both antecedents to and consequences of the individual's behavior [206]. Treating other aspects of disability, facilitating communication, and providing opportunities for enjoyable and productive activities can resolve some of the causes of disruptive behaviors, improve mood, and allow the person with TBI to feel more in control, with resultant decreases in aggressive and disruptive behavior. Along these lines, a review of approaches to social and behavioral dysfunction after acquired brain injury concluded that comprehensive holistic rehabilitation programs are more effective than both cognitive behavioral therapy (CBT) and applied behavioral analysis [207]. A patient's environment should be considered as well, including reduction of physical barriers to function and addressing the influences of those around him or her who may be provoking antisocial behavior. Behavioral interventions to address aggressive behavior should provide natural consequences (e.g., cleaning up and paying for broken items) whenever possible and should avoid reinforcing disruptive behavior. The individual must be taught alternative approaches to expressing him-/herself and getting his/her needs met [206]. Positive consequences for pro-social behavior can be put in place by exploring what would be rewarding to the person in question. Some programs use point systems or tokens that can be exchanged for rewards. There is a natural tendency for healthcare professionals and family members to pay attention to patients who are, for instance, shouting and shaking the bed rails or demanding something that cannot be provided. If, after addressing antecedents and consequences, a disruptive behavior continues, caregivers may have to give the patient "time-outs" from reinforcement of those disruptive behaviors [208]. To treat the executive dysfunction that is behind aggressive behavior, therapists must increase the awareness of the patient's own internal reactions by teaching self-monitoring techniques, providing feedback, and having them do self-evaluations. This type of training has been shown to result in decreased expression of anger and improved socialization in one study [209]. Paradoxically, the person's awareness of his or her reactions did not have to increase for the therapy to be effective. This finding requires verification. There is also limited evidence for the use of anger self-management training or psychoeducational treatment for anger and irritability [210].

At times, pharmacologic intervention is helpful. Treating underlying problems with arousal, initiation, and attentional disorders can have a secondary effect on irritability and disruptive behavior. Studies of methylphenidate to treat aggression ("off-label") have been of limited quality and mixed in their outcomes [211]. Treating depression and anxiety can also have an ameliorating effect on irritability and aggressive and disruptive behavior. The effect of antidepressants on aggressive behavior (not necessarily in the context of depression, therefore "off-label") has been studied, but the evidence for their efficacy is limited [211]. The pharmacologic treatment of aggression caused by disinhibition has been poorly studied [169], and all pharmacological uses are "off-label." Therefore, among the medications that may be useful for this condition, it is best to start with medications that have the fewest cognitive side effects. In a single-site, randomized, double-blind, placebo-controlled trial, amantadine has been demonstrated to reduce irritability and aggression at 28 days compared to placebo in a cohort of patients who were more than 6 months post-TBI [212]. In a large multicenter trial, participants in both the amantadine and placebo groups demonstrated improvements in observer-rated irritability at both 28 and 60 days; however, there were no between-group differences at either time interval [213].

Some anticonvulsants (valproic acid, carbamazepine, gabapentin, and lamotrigine) have been used for treating aggression and agitation [214]. However, there are no well-controlled studies demonstrating the efficacy of anticonvulsants [211, 215]. Levetiracetam can cause impulsive, irritable, and aggressive behavior [45]. There are studies suggesting that beta-blockers can be helpful [152]. It can take considerable time to reach therapeutic doses while the patient accommodates

to the changes in blood pressure and heart rate [211, 215]. Pindolol is a beta-blocker with partial adrenergic agonist effect (intrinsic sympathomimetic activity) such that it prevents blood pressure and heart rate from dropping below normal. In a small double-blind, placebo-controlled crossover study of people with ABI and severe aggressive behavior, it was found to significantly reduce aggressive behavior without causing sedation [216]. Beta-blockers have been found to cause cognitive decline in the elderly [217], and they can also cause fatigue and sedation [218]. Buspirone [211, 215] and lithium [169, 171, 219] have been used as well, although controlled studies in people with brain injury are lacking [211, 215]. The antipsychotics [169] can be used for more severe aggressive behaviors when other medications have not been effective or when relatively rapid control of behavior is needed because of the danger that someone will be harmed. There is some limited evidence for their efficacy in treating aggressive behavior [220]. However, they can cause Parkinsonian symptoms, dystonias, and tardive dyskinesia [211]. The atypical antipsychotics, which may have fewer motor side effects, can result in weight gain, dyslipidemia, and insulin resistance [221]. Both typical and atypical antipsychotics have been found to be associated with sudden death in elderly populations [222–224]. If they are to be used for an extended period of time, it is best to get a fasting blood sugar, lipid profile, and EKG before or shortly after starting them. Benzodiazepines are sometimes also used for situations in which relatively rapid control of aggressive behavior is needed. However, some authors believe that benzodiazepines can themselves cause disinhibition and agitated behavior [225]. As noted above, they can result in memory and attentional dysfunction and increase confusion. Even when they are helpful in the short term, this is often due to their sedating effect [211]. Their use can result in a pattern in which the patient is either sleepy or agitated. This results in other medications needing to be used to replace the benzodiazepine, and/or behavior plans must be put in place to reduce the aggressive behavior.

Social Support and Motivation

Social support is also an important element to success in rehabilitation, as it provides incentive and motivation to continue with what is usually a difficult ordeal. Motivation, but not physical capacity, is a strong predictor of physical activity levels in patients with TBI 6 weeks following discharge from inpatient rehabilitation [226]. Motivation and engagement are key to the success of rehabilitation, yet can be elusive, particularly following TBI when initiation, insight, or self-awareness is impaired [227]. Motivational interviewing, which is a nonconfrontational approach that allows the patient to take the lead and, thereby, fosters self-efficacy, can be effective with some individuals [228]. Bell and colleagues [229] found that a periodic telephone call that included motivational interviewing, counseling, education, and follow-up of various aspects of care resulted in improved functional outcomes and quality of life, although the results were not replicated in a multicenter randomized controlled trial [230].

Community Reintegration

Social, vocational, and community reintegration goals are important for individuals following TBI. Social communication abilities and behavioral functioning are factors that impact successful social integration post-TBI [231]. Return to work can be particularly challenging for individuals after TBI, and approximately 60% of working-age individuals (ages 16–60) remain unemployed at 2 years post-injury [232, 233]. Similarly, in an Australian study, only 44% of individuals remained employed within 3 years after moderate to severe TBI [234]. A systematic review identified access to transportation, access to services, participation in social interaction, the number of post-concussion symptoms (PCSs), fatigue, self-reported physical competence, subjective well-being, and pain to be possible predictors of employment outcomes [235]. Increased severity of TBI, older age, pre-injury psychological treatment, pre-injury student or

"blue-collar" employment, and pre-injury substance use are also associated with poor employment outcomes [232, 233, 236]. There may be a decline in the probability of post-TBI employment between 5 and 10 years post-injury [223, 233]. However, an Australian study showed an increase in employment between 2 and 5 years post-injury followed by a plateau from year 5 to year 10 [236]. Return to driving after TBI is also challenging, but can confer a large degree of independence if successful return to driving is achieved. Individuals with TBI who are driving a vehicle at 1-year follow-up are more likely to be employed at 2-year follow-up [237]. However, specific rehabilitation for return to driving with driving evaluations and road safety tests is often needed as the risk of involvement in traffic accidents with personal responsibility also increases after return to driving post-severe TBI [238].

The extent to which an employer is supportive following a TBI can be crucial to successful return to work for all severities. Vocational counselors can facilitate communication between the patient and the workplace. Therapies should attempt to simulate workplace tasks, although if the employer is cooperative, it may be better to return the person to work and have them coached and trained on the job. A gradual return to work can ease the transition [239]. Assistance with coordinating the return to work will often be needed, including on-the-job training and contact with the employer [240, 241]. The quality of studies on vocational interventions is low [242].

Caregiver Stress

Families of people with TBI are often under considerable emotional stress, especially when in caregiver roles [243–245]. Feelings of loneliness and caring for someone with severe disability are associated with higher caregiver burden [246]. Additionally, the presence of more functional impairment, neurobehavioral problems, and drug use in the TBI patient is associated with reduced caregiver life satisfaction in the first 2 years following injury [247]. The well-being of caregivers also has a reciprocal impact on the psychological well-being of those with TBI [248]. It is therefore important to educate caregivers about TBI and to provide them with lists of resources (e.g., brain injury associations, governmental programs, healthcare providers) that they may find useful so that they are equipped to cope with whatever issues arise. A randomized controlled trial of a telephone-based intervention comprised of individualized education and mentored problem-solving sessions focusing on the primary concerns of caregivers demonstrated improved caregiver outcomes with more active coping and less emotional venting [249]. Caregivers should also be encouraged to seek support via support groups, counseling, religious institutions, and friends [250, 251].

Mild Traumatic Brain Injury

Definition and Diagnosis

The definition of mild traumatic brain injury (mTBI) found in the literature has varied somewhat, but a widely used definition is that formulated by the Mild TBI Task Force of the American Congress of Rehabilitation Medicine [252]:

> a traumatically induced physiological disruption of brain function, as manifested by *at least* one of the following:
>
> 1) any period of loss of consciousness;
> 2) any loss of memory for events immediately before or after the accident;
> 3) any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and
> 4) focal neurologic deficit(s) which may or may not be transient;
>
> but where the severity of injury does not exceed the following: loss of consciousness of approximately thirty minutes or less; after thirty minutes, an initial Glasgow Coma Scale of 13-15; and posttraumatic amnesia not greater than 24 hours (Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine 1993).

Making the diagnosis of mTBI can be a difficult undertaking with a number of potential pitfalls. The patient's memory of or inferences about what occurred may be inaccurate. Medical records may not reflect a period of LOC or post-traumatic amnesia (PTA) that occurred before medical personnel arrived at the scene. The GCS may not have been assessed or reassessed until more than 30 min has passed. There is a potential problem with the overlap of the acute signs and symptoms of mTBI with acute stress reactions that commonly cause people to be "dazed, disoriented, or confused" after a major physical and/or psychological trauma that may include a brush with death. The clinician must obtain the most objective information available (e.g., emergency medical records, accounts of observers), ask probing questions, and listen carefully to the patient's account and then use his or her judgment to sort out the etiology(ies) [253]. There are times when it is impossible to make the distinction between acute stress and mild TBI or both may have existed simultaneously. Neuroimaging such as diffusion tensor imaging (DTI), SPECT, and PET [254, 255] and serum or cerebrospinal fluid biomarkers such as S100B, neurofilament light, and tau protein are promising approaches to confirming that a patient has had a brain injury and/or that there is longstanding structural change [256]. However, there is disagreement among some studies; and additional work is needed to determine the ideal biomarker or combination of biomarkers with good sensitivity and specificity for brain injury, long-term cognitive impairment, and other persistent PCSs [255–257].

Post-concussion Symptoms

mTBI can be associated with a variety of symptoms; and the term "post-concussion syndrome" has frequently been used to describe the complex of cognitive, physical, and emotional complaints that can occur. Some have argued that these symptoms do not manifest in a specific set, but rather can occur in various combinations of one or two symptoms to many symptoms and should, therefore, not be referred to as a "syndrome" [258]. They are probably best referred to as "post-concussion symptoms" (PCSs) or "post-concussion disorders." That being said, most studies of PCSs use the "syndrome" as defined by one of the versions of the International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders, the Rivermead Post-concussion Symptom Questionnaire, or other survey instruments [259]. The most frequent complaints are fatigue, forgetfulness, difficulty concentrating, headaches, dizziness, irritability, insomnia, depression, and anxiety. They have been said to persist in 9–15% of people with mTBI [260, 261], but higher and lower estimates exist as well [262, 263]. These statistics depend very much on the number of symptoms that are required for inclusion, the timeframe for the use of the word "persistent," and the population studied [262]. Symptom frequency diminishes overtime, and it is controversial whether the symptoms can continue indefinitely or are the result of litigation or psychological factors when persistent. They can, of course, be seen in people with moderate or severe TBI and are in fact common complaints of people who have never had a TBI [264, 265]. A study of people with mTBI occurring 22–35 months earlier and sex- and age-matched controls who had presented to the emergency room with minor non-head injuries (also matched by time from injury) was done in Lithuania, where compensation is not much of an issue. It was found that there was no significant difference between the frequency of complaints that could be attributed to a TBI in the group that had mTBI compared with the control group, except for depression, alcohol intolerance, and worry about having a brain injury. However, there were trends toward more complaints of "sporadic memory problems" in the mTBI group ($p = 0.052$) and toward more frequent endorsement of "no concentration problems" in the control group ($p = 0.079$) [266]. In fact, most studies using controls with orthopedic injuries find that having had a mTBI does not predict persistent PCSs (usually said to be those symptoms that continue for at least 3 months), while pre-injury psychiatric history, early post-injury anxiety, and pre-injury physical health are

the best predictors of persistent symptoms [267–270]. Another study found older age, preexisting psychiatric conditions, lower education, injury caused by assault, extracranial injuries, and lower GCS were predictive of worse functional outcome [271]. Other studies have found persistent PCSs or persistent post-concussion syndrome to be associated with both pre- and post-injury psychological issues [264, 272–276]. Hou and colleagues studied patients who had a mTBI without a control group and found that risk of persistent post-concussion syndrome (by ICD-10 criteria) was associated with negative mTBI perceptions, stress, anxiety, depression, and all-or-nothing behavior. In a study by Wilk and colleagues [277], blast injuries in a military context that resulted in mTBI without loss of consciousness were not associated with PCSs 3–6 months after the injury, whereas TBIs with LOC were associated with headaches and tinnitus, but not other PCSs. In a population of active-duty marines, ever having had a concussion was associated with greater emotional distress, but not with persistent PCSs or cognitive impairment. However, having had multiple concussions was associated with greater emotional distress, persistent PCSs, and cognitive dysfunction [278]. Depression is a frequently associated condition. PCSs overlap with the symptoms of posttraumatic stress disorder (PTSD) [260, 262, 264, 272, 275]. This is a major issue in the treatment of military populations, many of whom have blast injuries. As noted above, this is complicated by the fact that acute stress reactions are probably the norm at the time of a blast injury, when the service member may have had a brush with death, may have had severe bodily injury such as loss of a limb, and may have seen other service members killed and/or injured around him or her. Military combatants are likely to feel "dazed" and perhaps confused from emotional trauma at such times. When screened at a later date [279], they may endorse these symptoms and be screened positive on that basis (without clinician confirmation) for mTBI, setting in motion a process that may result in an incorrect diagnosis and treatment if they are actually experiencing PTSD or depression or a combination of mTBI with one or more mental health disorders [260, 272, 275, 280]. The case can be made that some such people would never have sought help for their emotional struggles due to an inability to face their emotional problems and/or the stigma attached to mental health disorders. PTSD is to some extent preventable in people with mTBI with the use of cognitive behavioral therapy during the period of acute stress reaction [281]. mTBI and PTSD in the military are discussed in greater depth in Chaps. 13 and 15.

Studies have shown that healthy control subjects or controls with minor non-head injuries report the frequency of PCSs at a rate higher than what is retrospectively reported by people with mTBI to have been present before their injuries. This has been interpreted to indicate that people with mTBI tend to attribute to the injury symptoms that were in fact present beforehand [266, 282, 283].

It is important to recognize that many of the physical and emotional symptoms associated with mTBI can, themselves, result in cognitive impairment even outside the context of mTBI. Some of the cognitive complaints following concussion may therefore have their origin at least in part from pain, insomnia, depression, and anxiety [284].

Symptoms, such as headaches and dizziness, should be treated symptomatically (see in the following), particularly in the early weeks and months following an mTBI. However, if such symptoms, in particular the cognitive, persist beyond a few months in the absence of other contributing factors (e.g., older age, previous concussions, history of attention-deficit disorder or learning disability – see in the following), the treating clinician should consider a psychological contribution and/or exaggeration related to litigation. However, as is the case with conversion disorder, such diagnoses are often met with considerable resistance and may result in the patient looking elsewhere for care until finding someone who believes them. In the case of psychological etiology, it can be helpful to have a program addressing persistent PCSs that routinely includes a psychological treatment component [262] so that the patient with persistent PCSs can enter this program.

Similar to the questions surrounding the etiology of other post-concussion symptoms, rehabilitation following mTBI is associated with considerable controversy about the expectation for cognitive recovery. The controversy stems from the fact that most prospective, controlled studies of unselected populations that use neuropsychological testing as an outcome measure have indicated that recovery is completed by 3 months after a first uncomplicated concussion [261, 285–287]. Samples taken from outpatient clinics or those including participants in litigation are associated with cognitive impairment beyond 3 months [287], and clinicians frequently see patients with residual cognitive complaints that continue indefinitely, even among non-litigators. There is also a study that found slower processing speed in patients older than 18 compared with comparable controls with orthopedic injuries even 3 months after injury [288].

There is an argument to be made that indeed some people may have longstanding residual cognitive impairment as a result of mTBI apart from any other influences. If such mild impairment existed in one or several hundred people who had concussions, it might take thousands of subjects before a statistically significant effect could be seen in a controlled study or meta-analysis. The number of people who have concussions has been estimated by the CDC to be approximately 1,275,000 annually in the USA (75% of the 1.7 million TBIs) [289, 290], so that the few clinicians who treat large numbers of people with mTBI still might see such patients with persistent PCSs more than occasionally.

There are a few lines of evidence suggesting that concussion can cause such residual cognitive impairment: (1) Studies suggest that multiple concussions might cause permanent findings on neuropsychological testing [278, 291–294]. In order for this to be the case, there has to be a certain amount of neuronal loss in a single concussion that is additive with each new concussion. Of course, the neuronal loss from a single concussion may or may not be enough to cause cognitive impairment. (2) Similarly, people with preexisting learning disabilities are more likely to have lasting cognitive effects from multiple concussions [290]. (3) Concussion has been found to result in worse functional outcomes [295, 296] and to be more likely to cause permanent cognitive deficits in older adults [297], though there is a study suggesting the contrary [298]. This subject is in need of further investigation. (4) Some studies of DTI done in people with mTBI have demonstrated diminished axonal integrity months or years after the injury in some patients [23, 254, 299, 300]. Again, some degree of axonal loss can undoubtedly be incurred without an effect on cognition. Kraus and colleagues [23] found that there was an overlap between the degree of white matter disruption found in people with mTBI and that of people with moderate TBI. On the other hand, Ilvesmaki and coauthors [301] found that abnormal DTI findings were not associated with acute mTBI when patients were compared with age- and gender-matched controls. There were substantial abnormalities among the older control subgroups. (5) There have been studies that have looked at more subtle aspects of cognition after mTBI than are generally evaluated in the studies that showed no change. Dual-task paradigms in particular demonstrate differences in those with histories of concussion compared with controls without concussion. Pare and coauthors [302] and Tapper and coauthors [303] found that reaction time in a dual-task paradigm was still prolonged at 3 months post-injury compared with healthy controls. Another study found subtle learning differences in a sample of non-litigating, working people following mTBI compared with controls [304]. (6) There is evidence that there may be real differences in cognitive complaints of people who have had mTBI in the distant past compared with controls. One study of consecutive patients with mTBI 6 months after injury found fatigue, which could reflect additional attentional resources being mobilized to accomplish the same tasks, to be a more common complaint (32%) among those with mTBI than among controls with minor injuries [305]. The Lithuanian study cited above found trends toward complaints of memory and attention problems in people long after mTBI compared to controls [266]. With a greater number of subjects, these trends may have been significant.

It is possible that a very mild decline in cognitive capacity that would not be clinically significant for most people can play a larger role in the context of diminished cognitive reserve. The cognitive reserve hypothesis suggests that individuals with traits that are associated with lower cognitive function would have a worse cognitive outcome than others with the same injury [260, 306, 307]. As discussed above, among those with mTBI, previous concussions, preexisting learning disability, and older age may be risk factors for persistent neuropsychological decline. As also discussed above, other factors that affect cognition, such as sleep disorders (e.g., insomnia, sleep apnea), persistent pain, or psychological factors (e.g., depression, PTSD), can diminish cognitive reserve such that a mTBI would result in persistent neuropsychological deficits that may not otherwise have been manifested [306]. There is probably a spectrum of patients with respect to persistent cognitive complaints:

1. On one end of the spectrum would be those who had more axonal injury than is typical for a mTBI and whose cognitive deficits result largely from brain injury. Those with GCS scores of 13 may be in this category, though it is possible to have a higher score and still have a more severe injury than is usual.
2. Those patients who have diminished cognitive reserve for any of the variety of reasons discussed above, but who also have significant enough axonal injury to interact with this diminished reserve to result in increased cognitive impairment.
3. Those patients who are otherwise like those in 2 above, but whose recovery is such that they no longer would have significant cognitive disorder were it not for the issues causing diminished cognitive reserve.
4. On the other end of the spectrum are those who had no or insignificant axonal injury and whose cognitive problems result entirely from other causes such as insomnia, chronic pain, or psychological diagnoses. It is often quite difficult to be certain where the patient falls in this spectrum.

Rehabilitation of PCSs

Studies of early preventive interventions after mTBI show inconsistent results [308, 309]. There are some reports suggesting that an educational process improves the outcome in patients with mTBI [310–312]. An RCT found that a telephone intervention providing information about mTBI, assistance with strategies for managing symptoms, and resources in case of problems was associated with a reduction in symptoms at 6 months after injury compared with care as usual [313]. In a single-blind RCT of patients with TBI, mostly on the milder side, a telephone follow-up for advice and referral as needed 7–10 days following injury improved social disability and reduced PCSs compared with a control group with no specific intervention. Subgroup analysis demonstrated benefit only in those with length of PTA of less than 7 days [2, 314]. However, another study of patients with mTBI found no difference in PCSs at 1 year between those who received a telephone call or letter with advice and referral for rehabilitation as needed 2–8 weeks after injury and those with no intervention. In the intervention group, those with few PCSs declined rehabilitation and returned to work. Those with several PCSs accepted rehabilitation, but had not recovered after 1 year [315]. A single-blind RCT of all patients with mTBI presenting to the hospital found that there was no difference in the change in symptoms, community skills, or self-perception of general health among those who received rehabilitation interventions as needed vs. education (including that a good outcome could be expected) and advice [2, 316].

Although it may or may not prevent later symptoms, as with any disease process, patients should be educated about their illness. The patient can be told that dizziness, headaches, insomnia, cognitive impairment, and other PCSs are also likely to resolve overtime and that pain, emotional factors, and insomnia can exacerbate or cause cognitive impairment. If the symptoms, including cognitive problems, have been continuing for more than 10–14 days, it may be worthwhile to validate any anxiety that may be present by cautioning the patient that it is usually

stressful to experience these symptoms, especially cognitive dysfunction, and that this stress can itself further exacerbate the symptoms. Such education is as much an art as a science at this point in time.

When one suspects that an extended recovery is possible due to psychological issues, it may help to take it a step further and tell the patient that some people with PCSs experience a protracted course of recovery as a result of the stress involved and that if the recovery takes more than a few months, psychological issues are a possible cause and should be addressed in greater depth at that time. Having anticipated this process makes it easier to broach the subject of psychological issues at a later date, whereas patients can be otherwise quite resistant to accepting a psychological etiology for their symptoms. Having normalized the possible emergence of psychological problems will make it easier for patients to confront their anxious or depressive feelings and to accept treatment if they do occur.

Although it is probably the most commonly prescribed early intervention, there is little evidence that bed rest is helpful, and in fact it may be harmful [270, 317, 318]. Complete cessation of activity is almost impossible to adhere to and can result in anxiety, depression, and deconditioning. Patients should be encouraged to return to activities as tolerated, and follow-up should be scheduled in case of difficulty [270].

As noted above (see "Behavioral and Emotional Disorders"), cognitive behavioral therapy can be successful in treating anxiety and depression following TBI, including mTBI [319]. Symptoms such as dizziness may be influenced by cognitive behavioral therapy [320]. A study of individual cognitive behavioral psychotherapy combined with cognitive remediation in participants with persistent PCSs found that those in the experimental group showed better emotional functioning and also did better on a measure of divided attention than a waitlist control group [321]. Although not yet studied in mTBI, contextual behavior therapy and acceptance and commitment therapy are preferred by one group [262, 283]. As noted (see "Behavioral and Emotional Disorders"), if pharmacological intervention becomes necessary, depression is best treated with the SSRIs and the non-sedating SNRIs. Anxiety can be treated with these medications as well. However, a meta-analysis of controlled trials of both pharmacologic and non-pharmacologic interventions for depression following mTBI found that in fact, overall, controls did significantly better than the experimental groups [322].

If cognitive symptoms do persist, patients may benefit from cognitive rehabilitation to learn strategies for managing problems with arousal, attention, memory, and executive function (see "Cognitive Rehabilitation"). There is no published data to assist the clinician in determining if and when it is best to begin these interventions in people with mTBI, and there are no specific guidelines available. Clinicians must be careful not to contribute to some patients' exaggerated belief that the full extent of their cognitive problems is caused by brain injury [262]. Therapies should address the functional tasks that the individual is involved in in everyday life and may need to include community outings. Pharmacological interventions can be helpful (see "Cognitive Rehabilitation"), and again there is no information available on the timing of such treatment. Foam earplugs and sunglasses can be tried for those sensitive to noise and light, respectively [323]. When sleep apnea is contributing to attention or arousal problems, positive airway pressure therapy or a custom oral device designed to open the airway is indicated. Insomnia is also a common contributor to cognitive symptoms following mTBI. See Chap. 7 for a discussion of sleep disorders following TBI. Endocrine dysfunction should also be addressed if present. See Chap. 11 for a discussion of endocrine disorders after TBI.

As noted above, if PCSs persist beyond a few months, psychological intervention may be indicated, whether for assistance with reactive depression and anxiety or for preexisting issues. Instruction on sleep hygiene should be given for those with insomnia. Relaxation techniques can be helpful as well. Clinicians should continue to educate the patient and significant others with respect to the interaction between the cognitive, psychological, and physical sequelae. Support

groups are often useful. Family counseling is indicated when there is evidence of stress on family members or dysfunctional family dynamics.

There are several common types of posttraumatic headaches, and in any given individual, more than one can be at play [273, 324–327]. They should, therefore, be addressed on multiple levels, with the emphasis depending on the headache type. When patients have tension headaches, treating problems with attention, sleep disorders, and psychological stresses may reduce symptoms. Patients with myofascial pain originating in the neck, upper back, or temporomandibular (TMJ) joints generally benefit from physical therapy, including stretching and strengthening exercises; postural retraining; trigger point massage; modalities such as heat or cold (some respond better to one or the other) or electrical stimulation; electromyographic biofeedback; or massage. A workplace or other environmental evaluations can identify remediable factors that may be contributing. Trigger point injections can be helpful, as can systemic pharmacological approaches (e.g., some antidepressants, gabapentin, milnacipran – all "off-label"). Patients with TMJ problems can be treated with myofascial techniques, mouth guards, and exercises. Those headaches with an apparent vascular component (e.g., migraine headaches) may respond to acetaminophen, NSAIDs, or vasoconstrictive agents commonly used to abort migraine headaches (e.g., sumatriptan); but overreliance on these agents can cause medication overuse headaches (MOH) ("rebound headaches"). Patients must be educated about MOH and told to restrict the use of such drugs for the worst headaches if they are frequent. For prophylaxis, some beta-blockers (e.g., propranolol), calcium channel blockers (e.g., verapamil), antidepressants (e.g., amitriptyline, nortriptyline, venlafaxine), and anticonvulsants (e.g., valproic acid, gabapentin, topiramate) can be helpful (all "off-label"). Topiramate may be the most effective medication for prevention of migraine headaches, though it should be used cautiously due to its propensity to cause cognitive problems (see "Pharmacological Treatment of Cognitive Disorders"). Tension headaches may respond to some of these agents as well, though not to calcium channel blockers. Injection of local anesthetics and/or corticosteroids can be considered for greater or lesser occipital neuralgia that does not respond to more conservative approaches. Injection should be done at the site along the nerve that replicates the headache when palpated [325, 326, 328]. Botulinum toxin injections into pericranial musculature can be used for migraine prophylaxis, though may have only marginal benefit [329]. There may also be a role for botulinum toxin injections as prophylaxis against rebound headaches ("off-label") [330]. See Chap. 9 for further discussion of the treatment of headaches following TBI.

Dizziness following mTBI is often of the vertiginous type, with sensations of spinning or, more commonly, movement. Repositioning maneuvers can provide relief from benign paroxysmal positional vertigo by displacing and dispersing canaliths [331, 332]. When vertiginous dizziness persists beyond 3 months, exercise-based vestibular rehabilitation can bring about CNS accommodation under controlled circumstances, thus reducing symptoms [331]. The therapist can also instruct the patient in learning compensatory strategies when accommodation is not successful [333]. Cervicogenic dizziness is addressed by treating the underlying cervical musculoskeletal dysfunction. Suppressive medications (e.g., clonazepam, scopolamine, meclizine, gabapentin), if used at all, should only be tried when other approaches have failed [334]. The evidence for their efficacy is extremely limited, and some of them can cause an exacerbation of problems with attention and memory. Occasionally perilymph fistula is the cause of persistent vertigo, but the diagnosis is difficult to make. Pressure-induced vertigo or disequilibrium and sensorineural hearing loss are often present. The outcomes with respect to vertigo are reported to be good in 82–95% of cases, but only case series have been published. Recurrence rates are reported at 8–27%, but others believe the recurrence rate is considerably higher, as much as 67% [335–339]. See Chap. 8 for further discussion of vestibular disorders.

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