INTRODUCTION

Every year, at least 1.7 million traumatic brain injury (TBI) occur either as an isolated injury or along with other injuries. [1]

Systems of care for patients with TBI must account for the particular characteristics of this disorder:-

- First, TBI is among the most common of serious, disabling neurological disorders. It is a significant problem in all societies.[2]
- Second, TBI is largely a younger and older person's disorder, Individuals younger than 30, mostly males, make up the largest proportion of those affected.[3]
- Third, TBI commonly affects people with preexisting problems such as substance abuse, learning disabilities, behavioral disorders and other risk factors that may make people more prone to injuries.[3]
- Fourth, the most important and consistent effects of TBI involve cognitive, emotional, and behavioral functioning. Motor and sensory perceptual problems also occur in varying amounts. Cognitive and behavioral problems present more challenges to the health care system because they are often more difficult to recognize, characterize, and treat than traditional medical and physical problems.[4]
- Finally, TBI is a disorder with a wide variety of pathophysiological effects, a range of severities, and a multitude of problems that may occur as the result of injury. Persons with apparently similar injuries may have significant variation in their presentation, course of recovery, response to interventions and ability to return to functioning.[5]

Thus, systems of care for TBI need to recognize the potentially prolonged recovery timetable. Further, recovery after TBI has a somewhat predictable and characteristic course, with a variety of recognizable cognitive, behavioral, and sensorimotor syndromes at different stages.

An understanding of brain injury, its clinical consequences, associated problems and complications, and natural history of recovery helps in applying proper services for patients along the continuum of care, and helps assure more effective use of resources.[6]

REVIEW OF LITERATURE

Traumatic brain injury (TBI)

Definition of TBI

The main difficulty with defining TBI is differentiating between those people who have had a head injury (a definite episode of external force to the head, including a deceleration force without actual impact to the head), and those who also have TBI. Most international definitions of TBI require some neurological symptoms or signs such as loss of consciousness, a period of amnesia and or focal neurological deficit. [7]

TBI is defined as damage to the brain resulting from external mechanical force, such as rapid acceleration or deceleration, impact, blast waves, or penetration by a projectile. [8] Brain function is temporarily or permanently impaired and structural damage may or may not be detectable with current technology.[9]

Classification of TBI

TBI is usually classified based on severity, anatomical features of the injury, and the mechanism (the causative forces). [10]

Brain injuries can be classified into mild, moderate, and severe categories. [10] The Glasgow Coma Scale (GCS), the most commonly used system for classifying TBI severity, grades a person's level of consciousness on a scale of 3–15 based on verbal, motor, and eye-opening reactions to stimuli. It is generally agreed that a TBI with a GCS of 13 or above is mild, 9–12 is moderate, and 8 or below is severe.[9]

Mechanism related classification divides TBI into closed and penetrating head injury. [8]A closed injury occurs when the brain is not exposed. Penetrating or open head injury occurs when an object pierces the skull and breaches the duramater, the outermost membrane surrounding the brain. [11]

Damage from TBI can be focal or diffuse, confined to specific areas or distributed in a more general manner, respectively. However, it is common for both types of injury to exist in a given case. [12]

Diffuse injury manifests with little apparent damage in neuroimaging studies, but lesions can be seen with microscopy techniques post-mortem [12] and in the early 2000s, researchers discovered that diffusion tensor imaging (DTI), a way of processing MRI images that shows white matter tracts, was an effective tool for displaying the extent of diffuse axonal injury.[13] Types of injuries considered diffuse include edema (swelling) and diffuse axonal injury, which is widespread damage to axons including white matter tracts and projections to the cortex. [14]

Research shows that the most common areas to have focal lesions in non-penetrating traumatic brain injury are the orbitofrontal cortex and the anterior temporal lobes, areas that are involved in social behavior, emotion regulation, olfaction, and decision-making, hence the common social/emotional and judgment deficits following moderate to severe TBI. [15]

One type of focal injury, cerebral laceration, occurs when the tissue is cut or torn. [16] Such tearing is common in orbitofrontal cortex in particular, because of bony protrusions on the interior skull ridge above the eyes. [15]

Mechanism of TBI (Fig.1)

The type, direction, intensity, and duration of forces all contribute to the characteristics and severity TBI [8] Forces that may contribute to TBI include angular, rotational, shear, and translational forces.[16]

Even in the absence of an impact, significant acceleration or deceleration of the head can cause TBI; however in most cases a combination of impact and acceleration is probably to blame.[16]

Forces involving the head striking or being struck by something, termed contact or impact loading, are the cause of most focal injuries, and movement of the brain within the skull, termed noncontact or inertial loading, usually causes diffuse injuries. [17]

In impact loading, the force sends shock waves through the skull and brain, resulting in tissue damage, Shock waves caused by penetrating injuries can also destroy tissue along the path of a projectile, compounding the damage caused by the missile itself. [18]

Damage may occur directly under the site of impact, or it may occur on the side opposite the impact (coup and contrecoup injury, respectively). [19] When a moving object impacts the stationary head, coup injuries are typical[20] while contrecoup injuries are usually produced when the moving head strikes a stationary object. [21]

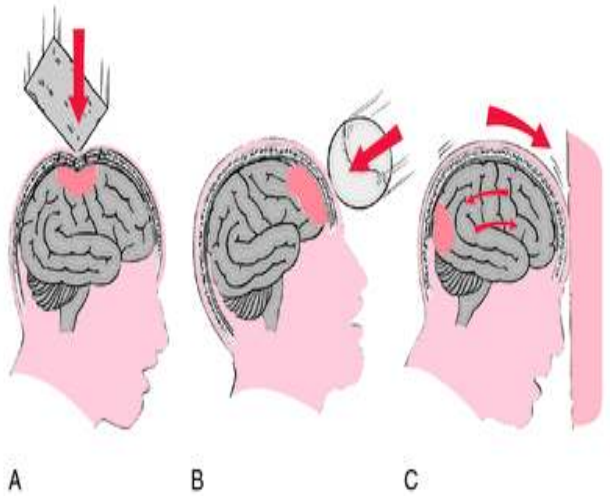

Figure (1): Some mechanisms of head injury. Head injury results from penetration or impact. (A) A direct injury (blow to skull) may fracture the skull. Contusion and laceration of the brain may result from fractures. Depressed portions of the skull may compress or penetrate brain tissue. (B),a blow to the skull may cause the brain to move enough to tear some of the veins going from the cortical surface to the dura. Subsequently, subdural hematoma may develop. Note the areas of cerebral contusion (shaded in red). (C) Rebound of the cranial contents may result in an area of injury opposite the point of impact. Such an injury is called a contrecoup injury. [22]

Pathophysiology

Primary and secondary TBI

Primary and secondary TBI are ways to classify the injury processes that occur in brain injury. Primary injury occurs during the initial insult, and results from displacement of the physical structures of the brain. On the other hand, secondary injury occurs gradually and may involve an array of cellular processes.[23] Secondary injury, which is not caused by mechanical damage, can result from the primary injury or be independent of it. [24]

Primary TBI

In TBI, primary injuries result immediately from the initial trauma. [25] Primary injury occurs at the moment of trauma and includes contusion, damage to blood vessels, and axonal shearing, in which the axons of neurons are stretched and torn, the blood brain barrier and meninges may be damaged in the primary injury, and neurons may die. [26]

Cells are killed in a nonspecific manner in primary injury, Tissues have a deformation threshold: if they are deformed past this threshold they are injured. [27]

Different regions in the brain may be more sensitive to mechanical loading due to differences in their properties that result from differences in their makeup; for example, myelinated tissues may have different properties than other tissues. Thus some tissues may experience more force and be more injured in the primary injury. The primary injury leads to the secondary injury. [27]

The initial injury to the brain produces a series of cellular events contributing to a neurochemical and neurometabolic cascade. [28] (Fig.2)

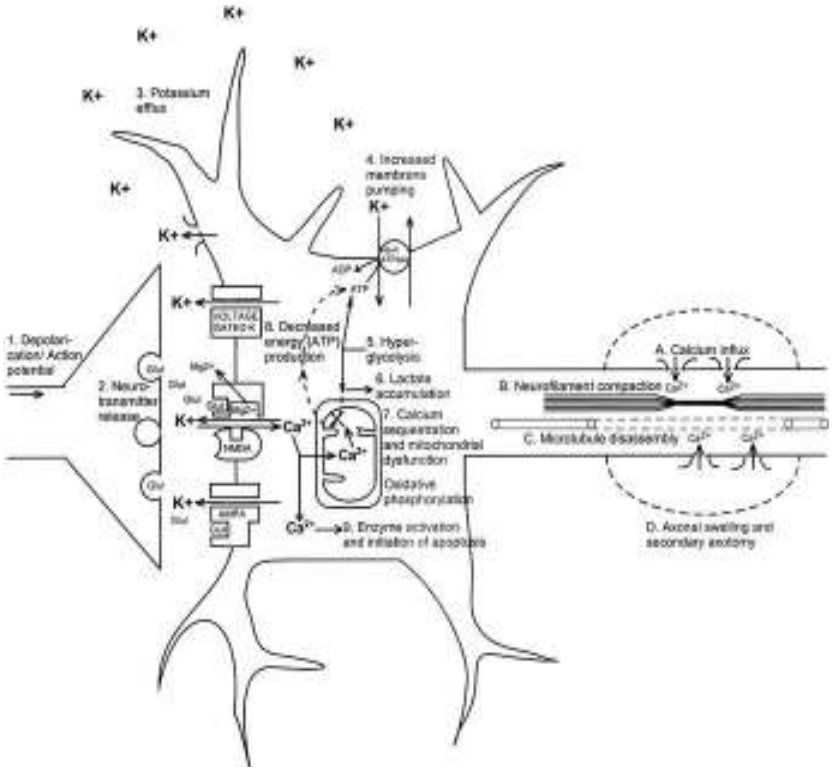

Figure (2): Neurometabolic cascade following traumatic injury. 1) Depolarization and initiation of action potentials. 2) Release of excitatory neurotransmitters. 3) Massive efflux of potassium. 4) Increased activity of membrane ionic pumps to restore homeostasis. 5) Hyperglycolysis to generate ATP. 6) Lactate accumulation.7) Calcium influx and sequestration in mitochondria leading to impaired oxidative metabolism. 8) Decreased energy (ATP) production. 9) Calpain activation and initiation of apoptosis. [29]

This cascade is set off initially, at least in part, by focal disruption of axonal transport. The ionic influxes activate genes and oxygen radicals, and then cell membrane lipid peroxidation occurs very early after injury. In turn, free intracellular calcium is increased and phospholipases are activated. These further damage the membrane and cytoskeleton and block axoplasmic transport. This can result in delayed cell death or trigger apoptosis. [30]

Excess quantities of glutamate in the extracellular space may lead to uncontrolled shifts of sodium, potassium, and calcium, which in turn disrupt ionic homeostasis. This may lead to severe cell swelling and subsequent cellular death. [31] (Fig.3)

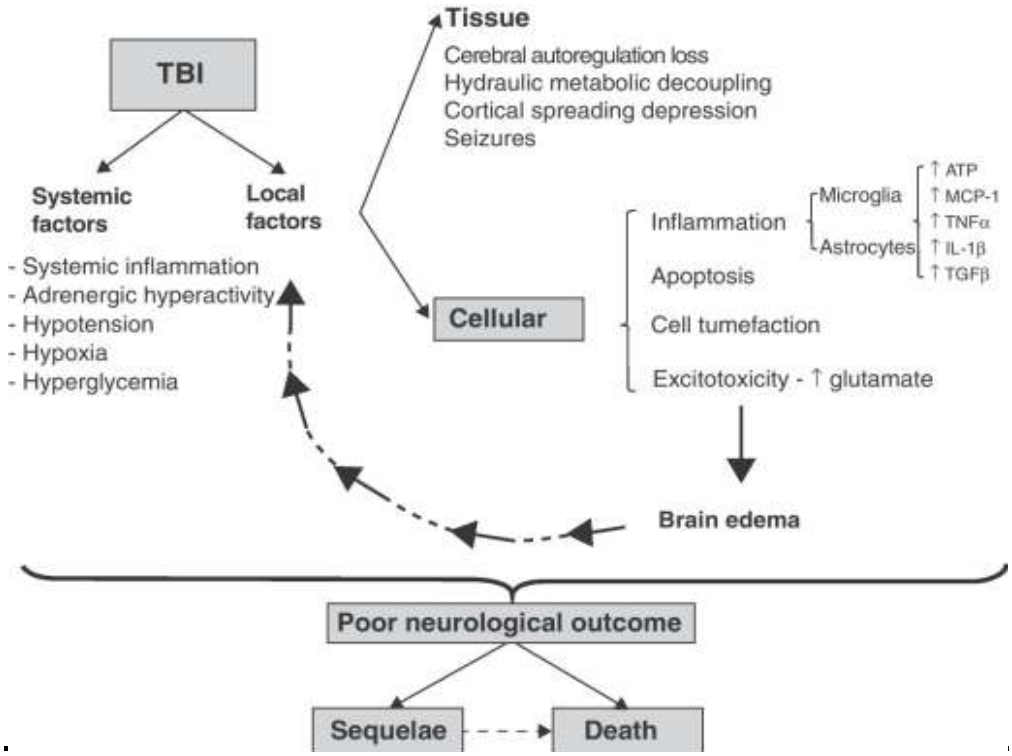

Figure (3): Cellular and molecular mechanisms involved in TBI. [32]

Secondary TBI

Secondary injury is an indirect result of the insult. It results from processes initiated by the trauma; it occurs in the hours and days following the primary injury and plays a large role in the brain damage and death that result from TBI.[33]

Unlike in most forms of trauma a large percentage of the people killed by brain trauma do not die right away but rather days to weeks after the event.[34] In addition, rather than improving after being hospitalized as most patients with other types of injuries do, about 40% of people with TBI deteriorate.[35]

Secondary injury can result from complications of the injury. These include ischemia; cerebral hypoxia; hypotension; cerebral edema; changes in the blood flow to the brain; and raised intracranial pressure. If intracranial pressure gets too high, it can lead to deadly brain herniation, in which parts of the brain are squeezed past structures in the skull. [23]

Other secondary insults include hypercapnia, acidosis, meningitis, and brain abscess. In addition, alterations in the release of neurotransmitters can cause secondary injury. Imbalances in some neurotransmitters can lead to excitotoxicity, damage to brain cells that result from over activation of biochemical receptors for excitatory neurotransmitters. [36]

Excitotoxicity can cause a variety of negative effects, including damage to cells by free radicals, potentially leading to neurodegeneration. Another factor in secondary injury is loss of cerebral autoregulation, the ability of the brain's blood vessels to regulate cerebral blood flow. [36]

Dopaminergic systems in TBI

Inside the brain, dopamine (DA) plays important roles in motor control, motivation, arousal, cognition, and reward, as well as a number of basic lower-level functions including lactation, sexual gratification and nausea. [37]

Dopaminergic neurons (i.e., neurons whose primary neurotransmitter is dopamine) are comparatively few in number a total of around 400,000 in the human brain and their cell bodies are confined to a few relatively small brain areas, but they send projections to many other brain areas and exert powerful effects on their targets. [37]

These dopaminergic cell groups were first mapped in 1964 by Annica Dahlström and Kjell Fuxe, who assigned them labels starting with the letter "A" (for "aminergic").

In their scheme, areas [A1] through [A7] contain the neurotransmitter norepinephrine, whereas [A8] through [A14] contain DA.

Here is a list of the dopaminergic areas they identified :[38] (Fig.4)

- The substantia nigra: play important roles in motor control. These neurons are especially vulnerable to damage. When a large fraction of them die, the result is a Parkinsonian syndrome. [39]
- The ventral tegmental area (VTA), play a central role in reward and other aspects of motivation. [40]
- The posterior hypothalamus. There is some evidence that pathology in this area plays a role in restless legs syndrome. [41]
- The arcuate nucleus it influences the secretion of the hormone prolactin. [42]
- The zona incerta. Participate in the control of gonadotropin-releasing hormone. [42]

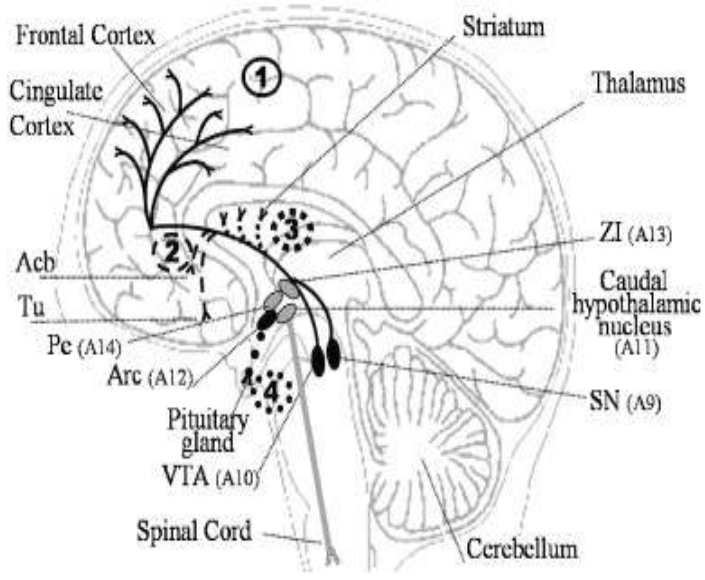

Figure (4): Anatomical representation of the main dopaminergic pathways in human. [43]

DA receptors are abundantly expressed in brain areas known to be damaged after TBI, such as the frontal cortex and striatum, which are important for cognitive function. [44]

Alterations in Dopaminergic systems after TBI

Evidence that Dopaminergic systems are altered in humans after TBI is predominantly based on reports that neurostimulants are beneficial in attenuating cognitive deficits and data showing altered DA transporter binding after TBI, Donnemiller et al[45] used single photon emission computed tomography (SPECT) to show that striatal DAT binding is decreased in patients 4–5 months after severe TBI, even in cases where no anatomical evidence of direct striatal injury exists.[45]

After experimental TBI, alterations in catecholamine systems have been found in various brain regions and have been shown to be time dependent. For example, transient increase in DA in both the striatum up to 6 hours and the hypothalamus up to 24 hours has been identified utilizing microdialysis. [46]

Tissue DA levels were also elevated in both the ipsilateral and contralateral striatum at 1 h compared to same animals. [47]

Increases in human cerebrospinal fluid (CSF) DA and its metabolites post-TBI have been shown to depend on both gender and genetic variations in the DA transporter (DAT). Furthermore, the systemic administration of DA as an inotropic agent in TBI patients was also associated with higher CSF DA.[48]

Implications of Acute Dopamine Increases Following TBI

Dopamine and Cell Death

DA is carefully regulated by the CNS and alterations can lead to significant cellular dysfunction and/or death. [49]

Dysregulation of DA levels or death of DAergic neurons that induce low DA states can lead to some of the symptoms of schizophrenia and Parkinson's disease. [50]

Conversely high levels of DA are also implicated in symptoms associated with schizophrenia and cause significant dysfunction in working memory (WM) and learning.[51]

Dopamine and CNS Inflammation

Strategies to reduce neuronal inflammation in TBI have provided benefits in neuronal sparing and functional outcomes.[52] However, difficulties remain due to concerns over the potential neuroprotective role of inflammatory cells and worries over what side effects direct inhibition of inflammation may cause.[53]

DA can act as a potent inflammatory agent within the CNS. In Parkinson's disease it has long been known that excessive DA or glutamate can induce a pro-inflammatory environment. [54]

There is also recognized vulnerability of DAergic neurons to the inflammatory cascade [55], which may be partially explained by the fact that microglia possess DA receptors that appear to stimulate migration and activation to DAergic brain regions. [56]

It has also been shown that drugs with DAergic action can reduce inflammation (e.g. buproprion) within the CNS. [57]

This suggests that while endongenous DA can activate inflammatory pathways, activation of DA receptors with therapeutics may still provide reductions in inflammation. This dual nature of DAergic signaling also demonstrates the complexities of DAergic signaling that need to be better understood as therapies targeting DA move towards clinical application.[57] (Fig.5)

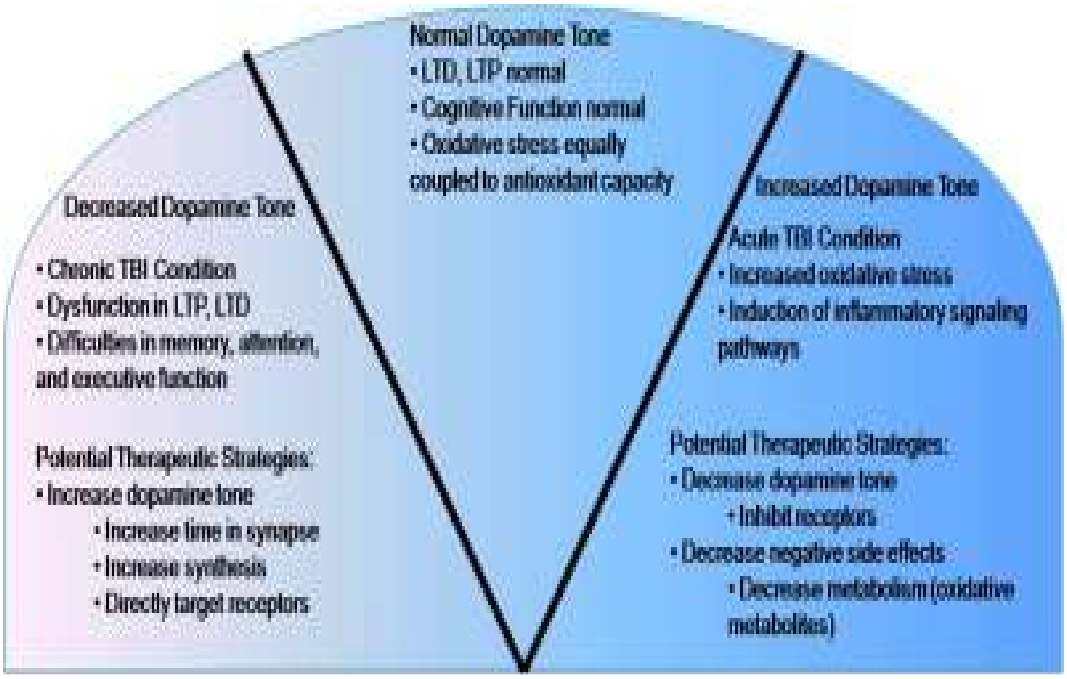

Figure (5): Dopamine (DA) is a tightly regulated system that has potential negative consequences with increased or decreased dopaminergic tone. Several studies assessing DA report an increase immediately after TBI and a significant decrease at later stages. Therapeutic strategies should consider the implications of this bi-phasic response in DA systems after TBI. [58]

Signs and symptoms of TBI

Symptoms are dependent on the type of TBI (diffuse or focal) and the part of the brain that is affected.[59]

Unconsciousness tends to last longer for people with injuries on the left side of the brain than for those with injuries on the right. Symptoms are also dependent on the injury's severity, with mild TBI the patient may remain conscious or may lose consciousness for a few seconds or minutes.[60]

Other symptoms of mild TBI include headache, vomiting, nausea, lack of motor coordination, dizziness, difficulty balancing, lightheadedness, blurred vision or tired eyes,

ringing in the ears, bad taste in the mouth, fatigue or lethargy, and changes in sleep patterns. Cognitive and emotional symptoms include behavioral or mood changes, confusion, and trouble with memory, concentration, attention, or thinking. Mild TBI symptoms may also be present in moderate and severe injuries. [60]

A person with a moderate or severe TBI may have a headache that does not go away, repeated vomiting or nausea, convulsions, an inability to awaken, dilation of one or both pupils, slurred speech, aphasia, dysarthria, weakness or numbness in the limbs, loss of coordination, confusion, restlessness, or agitation. [61]

Common long-term symptoms of moderate to severe TBI are changes in appropriate social behavior, deficits in social judgment, and cognitive changes, especially problems with sustained attention, processing speed, and executive functioning. [61]

Alexithymia, a deficiency in identifying, understanding, processing, and describing emotions occurs in 60.9% of individuals with TBI. Cognitive and social deficits have long-term consequences for the daily lives of people with moderate to severe TBI, but can be improved with appropriate rehabilitation.[62]

Diagnosis of TBI

Diagnosis is suspected based on lesion circumstances and clinical evidence, most prominently a neurological examination, for example checking whether the pupils constrict normally in response to light and assigning a Glasgow Coma Score. Neuroimaging helps in determining the diagnosis and prognosis and in deciding what treatments to give. [63]

The preferred radiologic test in the emergency setting is computed tomography (CT): it is quick, accurate, and widely available.

Magnetic resonance imaging (MRI) can show more detail than CT, and can add information about expected outcome in the long term. It is more useful than CT for detecting injury characteristics such as diffuse axonal injury in the longer term. However, MRI is not used in the emergency setting for reasons including its relative inefficacy in detecting bleeds and fractures, its lengthy acquisition of images, the inaccessibility of the patient in the machine, and its incompatibility with metal items used in emergency care.[64]

Management of TBI

It is important to begin emergency treatment within the so-called "golden hour" following the injury. People with moderate to severe injuries are likely to receive treatment in an intensive care unit followed by a neurosurgical ward. Treatment depends on the recovery stage of the patient. In the acute stage the primary aim of the medical personnel is to stabilize the patient and focus on preventing further injury because little can be done to reverse the initial damage caused by trauma. Rehabilitation is the main treatment for the subacute and chronic stages of recovery.[65]

Acute stage

Certain facilities are equipped to handle TBI better than others; initial measures include transporting patients to an appropriate treatment center. Both during transport and in hospital the primary concerns are ensuring proper oxygen supply, maintaining adequate cerebral blood flow, and controlling raised intracranial pressure (ICP), since high ICP deprives the brain of badly needed blood flow and can cause deadly brain herniation. [66]

An accurate way to measure ICP is to place a catheter into a ventricle of the brain, which has the added benefit of allowing cerebrospinal fluid to drain, releasing pressure in the skull. [67]

Treatment of raised ICP may be as simple as tilting the patient's bed and straightening the head to promote blood flow through the veins of the neck. Hypertonic saline can improve ICP though it is used with caution to avoid electrolyte imbalances or heart failure. [8]

Diuretics, drugs that increase urine output to reduce excessive fluid in the system, may be used to treat high intracranial pressures, but may cause hypovolemia. [67]

Hyperventilation (larger and/or faster breaths) reduces carbon dioxide levels and causes blood vessels to constrict; this decreases blood flow to the brain and reduces ICP, but it potentially causes ischemia and is, therefore, used only in the short term. [9]

Administration of corticosteriods is associated with an increased risk of death, and so it is recommended that they not be given routinely. [68]

Hypotension which has a devastating outcome in TBI can be prevented by giving intravenous fluids to maintain a normal blood pressure. Failing to maintain blood pressure can result in inadequate blood flow to the brain. Blood pressure may be kept at an artificially high level under controlled conditions by infusion of norepinephrine or similar drugs, this helps maintain cerebral perfusion. [69]

Body temperature is carefully regulated because increased temperature raises the brain's metabolic needs, potentially depriving it of nutrients.[70] Seizures are common. While they can be treated with benzodiazepines, these drugs are used carefully because they can depress breathing and lower blood pressure. [71]

Traumatic brain injury may cause a range of serious coincidental complications which include cardiac arrhythmias and neurogenic pulmonary edema. [72] These conditions must be adequately treated and stabilised as part of the core care for these patients.

Decompressive craniectomy (DC) is performed routinely in the very short period following TBI during operations to treat hematomas; part of the skull is removed temporarily (primary DC). DC performed hours or days after TBI in order to control high intracranial pressures (secondary DC) has not been shown to improve outcome in some trials and may be associated with severe side effects. [73]

Chronic stage

Once medically stable, patients may be transferred to a subacute rehabilitation unit of the medical center or to an independent rehabilitation hospital. Rehabilitation aims to improve independent function at home and in society and to help adapt to disabilities and has demonstrated its general effectiveness, when conducted by a team of health professionals who specialise in head trauma. [74]

As for any patient with neurologic deficits, a multidisciplinary approach is key to optimising outcome. Physiatrists or neurologists are likely to be the key medical staff involved, but depending on the patient, doctors of other medical specialties may also be helpful. [74]

Pharmacological interventions for TBI

Depending on the location of injury, damage can occur to a variety of neurotransmitter networks critical to cognitive processes. Investigation has focused on the loss of dopaminergic neurons that regulate executive functioning, as well as deficits in norepinephrine and acetylcholine. [75]

Insufficient evidence exists to establish guidelines for optimal pharmocotherapy, medications may be used to support recovery. Examples are shown in table 1. [76]

- Acute phase (< 1 month post-TBI)
- Chronic phase(> 1 month post-TBI)

Table (1): Agents and indications to consider when managing sequelae of TBI.[76]

	Neuropsychiatric sequelae	**Neurocognitive sequelae**	**Neurobehavioral sequelae**	**Decreased level of consciousness**
Acute phase	selective serotonin reuptake inhibitors	Methylphenidate (attention, processing speed, memory deficits)	Amantadine (agitation, anxiety)	Bromocriptine (vegetative state)
		Amantadine (attention, concentration, alertness, mobility deficits)	selective serotonin reuptake inhibitors (anxiety)	Methylphenidate (coma, minimally conscious state
		Donepezil (attention, memory deficits)		Amantadine (minimally conscious state)
Chronic phase	selective serotonin reuptake inhibitors	methylphenidate (attention, memory deficits)	methylphenidate (agitation, impulsivity	bromocriptine (vegetative state, akineticmutism)
		modafinil (memory, motor, attention deficits)	amantadine (agitation, anxiety)	levodopa combined with carbidopa (vegetative state, coma)
	valproic acid	amantadine (attention, concentration, alertness deficits)	beta-blockers (agitation, aggression)	amantadine (minimally conscious state)

Amantadine

Amantadine was approved by the U.S. Food and Drug Administration in October 1966 as prophylactic agent against Asian influenza and eventually received approval for the treatment of Influenza virus A in adults. In 1969, the drug was also discovered by accident to help reduce symptoms of Parkinson's disease. [77]

Synthesis

Amantadine may be prepared by reacting adamantane with bromine or nitric acid to give the bromide or nitroester at position one, Reaction of either compound with acetonitrile affords the acetamide, which is hydrolyzed to give 1-adamantylamine. [78]

Pharmacokinetics

Amantadine is well absorbed orally. Maximum plasma concentrations are directly related to dose for doses up to 200 mg/day. Doses above 200 mg/day may result in a greater than proportional increase in maximum plasma concentrations.[79]

Amantadine is 90% excreted unchanged in the urine, and the elimination half-life is 9.7 to 14.5 hours. [80] Distribution is through all the tissues of the body, including the central nervous system. [81] and peak plasma concentrations occur 1 to 4 hours after ingestion. [82]

The elimination half-life increases two to three fold or greater when creatinine clearance is less than 40 mL/min/1.73 m2 and averages eight days in patients on chronic maintenance hemodialysis. Amantadine is removed in negligible amounts by hemodialysis. [79]

The pH of the urine has been reported to influence the excretion rate of Amantadine. Since the excretion rate of Amantadine increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase the elimination of the drug from the body. [79]

Mechanism of action

Amantadine appears to act through several pharmacological mechanisms

- The mechanism of Amantadine's antiviral activity involves interference with a viral proteinM2 which is required for the viral particle to become "uncoated" once taken inside a cell by endocytosis. [83]
- The mechanism of its antiparkinsonian effect is poorly understood. The drug has many effects in the brain, including release of dopamine and norepinephrine from nerve endings. It appears to be a weak N-methyl-D-aspartate receptor (NMDAR) antagonistas well as ananticholinergic, specifically a nicotinic alpha-7 antagonist like the similar pharmaceutical memantine.[84]
- Amantadine causes release of dopamine from central neurons, facilitates dopamine release by nerve impulses, and delays the reuptake of dopamine by neural cells. [85] It may also have profound (NMDAR) antagonist effects, which may contribute to its neuroprotective effects early after injury. [86]
- Amantadine has been demonstrated to increase the Homovanillic acid (HVA) levels in the CSF of animals. [87]It is generally accepted that amantadine acts presynaptically to enhance dopamine release and inhibit dopamine reuptake. [88] Patients who are using amantadine report feeling more alert or lively on the drug. [89]

Indications:

Parkinson's disease

Despite a 2003 Cochrane review of the scientific literature concluding that there is inadequate evidence to support the use of amantadine for Parkinson's, the drug continues to be prescribed for this indication.[90]

Influenza

Amantadine is no longer recommended for treatment of influenza A infection.For the 2008/2009 flu season, the United States' Centers for Disease Control and Prevention (CDC) found that 100% of seasonal H3N2 and 2009 pandemic flu samples tested have shown resistance to amantadine.[91]

Off-label uses

Amantadine is frequently used to treat the chronic fatigue often experienced by patients with multiple sclerosis.[92] Additionally, Limited data has shown that amantadine may help to relieve SSRI-induced sexual dysfunction.[93]

Adverse effects

The adverse reactions reported most frequently at the recommended dose of amantadine (5-10%) are: nausea, dizziness (lightheadedness), and insomnia.

Less frequently (1-5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, dry mouth, constipation, ataxia, livedo reticularis (mottled reticulated vascular pattern appears as a lace-like purplish discoloration of the skin), peripheral edema, orthostatic hypotension, nervousness, agitation, dry nose, diarrhea and fatigue. [94]

Infrequently (0.1-1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, skin rash, vomiting, slurred speech, euphoria, amnesia, hyperkinesia, hypertension, visual disturbance, corneal edema and optic nerve palsy. [94]

Rare (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, and suicidal attempt. [95]

Warnings

- **Deaths**

Deaths have been reported from overdose with amantadine. The lowest reported acute lethal dose was 1 gram. Acute toxicity may be attributable to the anticholinergic effects of amantadine. Drug overdose has resulted in cardiac, respiratory, renal or central nervous system toxicity. Cardiac dysfunction includes arrhythmia, tachycardia and hypertension [95]

- **Arrhythmia**

Amantadine has effects on cardiac electrophysiology, including prolongation of the action potential duration through inhibition of the influx of repolarising potassium ions, in rare cases, these effects can result in particular types of cardiac arrhythmia (apical reciprocating tachycardia or torsade de pointes arrhythmia), Treatment must be avoided or discontinued in patients who show baseline QTc values above 420 ms. [95]

- **CNS Effects**

Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity. [95]

- **Other**

Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving amantadine. [95]

How Supplied

One container of 500 ml infusion solution contains: Amantadine sulphate 200 mg, Sodium chloride, Water for Injections

As clear, colorless syrup [each 5 mL (1 teaspoonful) contains 50 mg amantadine hydrochloride] or as film coated tablets contains Amantadine sulphate 100 mg.

Recovery from TBI [96]

Recovery from a traumatic brain injury is a long, difficult process. It is emotionally draining for both the patient and the patient's family. Weeks and months may elapse before the patient is anywhere near their former self; progress to the best possible recovery may take years.

Ten myths of "recovery"

1: The Concept of "Recovery"

Most people's experience, and therefore expectations, regarding illness and injury is one of temporary reduction in functioning, followed by a gradual return to normalcy. People get sick, go to hospital, and get better. Bones are broken, casts applied for a period, muscle strength regained over several months, and scars fade. [97]

When commonplace notion of recovery is applied to head injury, however, considerable harm can be done. Almost never does a patient "recover;" the residual deficits are usually significant and permanent. The continual expectation of recovery can lead clients and families into denial, frustration, disappointment, and even worse, extremely unrealistic expectations and planning. [97]

2: Recovery Occurs in a Year

It was a traditional rule of thumb for physicians to tell patients and families that "whatever recovery will occur it will happen in the first 12 months." This was probably based on the observation that the neurological examination at one year was quite predictive of neurological status years later.[98]

The danger with the "recovery occurs within one year" myth is that it lulls families and professionals into thinking that the client's level of performance at one year is what everyone is stuck with. While the major brain healing may well have occurred within this time frame, true rehabilitation may just be beginning. [98]

3: The Concept of Plateau

Closely related to myth number two, this concept says that "recovery" starts after emergence from coma, continues at a gradual upward pace, then slows down, and levels off, so that no more improvement occurs. [99]

This myth leads families to despair when rate of change decreases and causes therapists to terminate services when clients stop progressing.

Head injured patients are notoriously inconsistent in their progress, at all stages. They may take one step forward, two back, do nothing for awhile, then unexpectedly make a series of gains. [100]

4: The Lourdes Phenomenon

This is often a side effect of subscribing to Myth of Recovery. The reference is to the town in France (Lourdes) where miraculous cures of illness are reputed to take place. There are many families who firmly believe that some "miracle" will occur after brain injury and return their loved one to normalcy (recovery).[101]

Belief in this myth often takes the form of "doctor hopping" or "program hunting." Families will put the head injured person through every available program or with every available therapist.

Despite any tangible signs of improvement, many will continue to believe that if only they could find the right person or right approach, everything would be better.[101]

The solution lies not in finding the right "cure", but in helping patients and families become aware of and accepting the limitations and developing new goals and expectations. [101]

5: The Normal IQ

Often, upon request, naive psychologists will examine a head injured person on a traditional battery of intelligence tests, find that the IQ is in the average range, and then pronounce the client "cognitively recovered", or "capable of functioning intellectually in the average range."[102]

This myth is dangerous because it can seriously misrepresent the client's deficits, and create unrealistic expectations in the minds of others that set the client up for serious failure. The conclusion is a myth for because an IQ score is a composite of many different scores. An overall IQ score can mask severe variability among performance levels; the person in the "average range of IQ" can be performing in the superior range on some tasks, but be severely impaired on others. [103]

6:The Normal Neurological Evaluation

Just as normal range IQ's should not be mistaken for cognitive normalcy, a normal neurological evaluation especially late after injury should not be mistaken as meaning that there is no brain dysfunction.

Also, because head injury is primarily a diffuse brain injury (i.e., involving damage at many scattered locations), it often is not possible to determine a neurological focus of damage as is the case after stroke or tumor (which affect primarily a single area in the brain). [104]

7: The Malingering

It is the exception, not the rule, to find clients who are consciously using their deficits to their advantage. The vast majority of head injured patients are extremely frustrated and very eager to get on with their lives.

Unfortunately, it is true that a learned dependency is often established; many head injured persons become so used to others doing for them, that they come to believe that they are incapable and must be dependent, and therefore resist efforts to get them to do more things on their own. Malingerers, however, become more resistant, not less, as they are forced to do more. Most head injured malingerers will probably show evidence of similar behaviors prior to their accident, and should be identified by sophisticated neuropsychological evaluation. [105]

8: The Disordered Life and the Need for Psychotherapy

Many people who enter traditional psychodynamic psychotherapy do so because they are dissatisfied with their lives. Their dissatisfaction may be due to being unsure of themselves, goals that are not clear, inability to accomplish what they want, unsatisfying relationships, anger or fear, or they are depressed. Psychotherapy offers them a chance to explore their feelings and past, uncover and resolve the conflicts that interfere with their lives, vent their frustrations, and get on with their lives.

Unfortunately, although many head injured persons fit the above description and thus get sent into traditional analytic or psychodynamic therapy they often get worse, not better, to everyone's dismay. This happens because the disorder in their lives reflects not primarily underlying psychological conflicts, but the damage to their brains that has resulted in cognitive and executive dysfunctions.

This does not mean that head injured persons cannot have mild or severe psychological problems that either result directly from, or exist (usually existed) separately from the results of their injury. (106)

9: The Drugs as Satans and Saviors

The other type of therapy susceptible to mythology is drug therapy,the use of drugs to treat various emotional, behavioral, and even cognitive problems after brain injury. This is a bipolar myth: The equally invalid myth that drugs are always bad (Satans) or the only possible cure (Saviors) for difficult problems after brain injury.

The Satanic myth holds that drugs can only do the head injured persons harm and should be avoided at all costs. This myth evolved from a basic truth: Many drugs given to brain injured persons have undesirable cognitive side effects and cause more harm than good. Certain antiseizure medications cause attention and memory problems, and choice of medication often does not reflect this awareness. For example Minor tranquilizers (such as Valium) which may calm anxious or tense persons without brain damage, may cause memory problems, poor judgment, and emotional control problems in head injured persons. (99)

Nevertheless, intelligent pharmacology instituted by someone who understands how the damaged brain reacts to drugs can be, when used in moderation, very helpful. Certain seizure medications have fewer cognitive side effects. Drugs that selectively block or enhance very specific neurotransmitter systems have the potential to decrease anxiety, lift depression, and perhaps (although this is still controversial) even enhance certain cognitive functions such as focused attention and memory, Drugs are dangerous, but not Satans. (107)

Nor are they Saviors, Occasionally professionals will encounter families who have heard claims made about new drugs that promise all manner of neurological, cognitive, and behavioral improvement, and latch onto such drugs as the "miracle" which will cure the problem. Often these are families who have suffered a long time with a difficult head injured family member, and who are having great difficulty coming to terms with the severity and permanence of the disability. No drug known will eliminate the problems of head injury. In general, less is better, but intelligent, selective use can be helpful. (108)

10: The Rehab Wizard

The Rehab Wizard practices a craft that goes by many names: cognitive remediation, cognitive rehabilitation, cognitive retraining, and others. The Wizard has a computer and an armful of software. They load a diskette, wave a magic mouse, and "presto" cognitive changes begin to occur. "Your client is unable to work because of memory deficits? No problem. Send him (or her) to the Wizard for a 10-week course of memory retraining, remediate that deficit, and back to work he'll (or she'll) go."Such cures don't happen of course. No professional has the wizardry to eliminate cognitive deficits due to damage to the brain. (103)

From Myth To Reality (96)

The myths aside, there are several concerns that truly are related to improvement following TBI, these include:

Severity

It is a common principle that the more severe the injury the less improvement can be expected. Severity is typically measured by length of coma (or Post Traumatic Amnesia), and the longer the coma, the more severe the injury. Recent research, however, suggests that while length of coma is related to severity of injury, it appears that the location of the injury is more important. For example, when the frontal lobes of the brain are moderately to severely damaged, regardless of length of coma, significant deficits in executive function are present. These deficits result in the inability to direct and regulate behavior and significantly interfere with returning to pre-injury lifestyles. (109)

Re-Morbid Characteristics

A number of pre-injury variables are associated with outcome. Those that appear to be most associated with "recovery" are pre-injury intelligence, cognitive abilities, and personality. (100)

Family

The TBI victim's family is critical to improvement in functional abilities. If the family is realistic in its expectations and provides sufficient structure, guidance, and support without fostering dependence, the likelihood of improvement is increased. (110)

Acceptance

The TBI victim's awareness of limitations and his ability to accept the fact that new life goals must be established has been found to be a critical variable, if not the most important variable, associated with successful outcome. (111)

Rehabilitation

The type and extent of rehabilitation following TBI is directly related to improved functional abilities. In years past, rehabilitation was discontinued when the individual was medically stable and could be discharged to his home or a nursing home. Later, rehabilitation was extended and focused on improving the person's physical abilities, e.g., walking and talking. Today, rehabilitation is available to address the hidden cognitive and emotional deficits that can hinder independent living. (111)

Support

Another critical variable associated with long term recovery is the support available in the victim's home community. Many TBI victims will require lifelong support to live and work in the community. The extent to which support is available, in terms of supported employment, supervised living, TBI support groups, TBI intervention, and outreach programs, increases the chances of success.(112)