

Long-Term Neuropsychiatric Disorders After Traumatic Brain Injury

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1. Introduction

The long-term neuropsychiatric consequences of traumatic brain injury are numerous and outstrip their physical counterparts in terms of impact on quality of life and outcomes such as return to work. This chapter will describe the epidemiology, pathology and investigation of brain injury, with a focus on findings that have particular relevance to neuropsychiatric disorders. A discussion of the difficulties in understanding aetiology in the neuropsychiatry of mild traumatic brain injury (mTBI), including postconcussional syndrome, will be undertaken alongside a broader overview of the key predisposing factors for long term psychiatric presentations. A review of the current understanding of post-TBI neuropsychiatric disorder including personality change; cognitive disorders and dementia; aggression; affective and anxiety disorders; and psychosis will highlight controversies in the literature. Finally, a summary of pharmacological interventions and practical treatment recommendations based on the best available evidence and clinical utility is described.

2. Epidemiology and definitions of Traumatic Brain Injury

Traumatic brain injuries (TBI) cause significant disability and have a considerable impact on those who suffer them, as well as their carers, medical services and the economy in general. It has been estimated that the annual cost of acute and chronic care for patients with TBI in the United States is in the region of \$60 billion and that the overall cost is in the region of \$200 billion each year, when medical, work loss and quality of life costs are taken into account (Finkelstein *et al.* 2006)

The Centers for Disease Control (Faul *et al.* 2010) estimated that there were 1.7 million TBI's in the United States (580 per 100,000) between 2002 and 2006. Of these, 1.3 million attended accident departments; 275,000 were hospitalized (93.8 per 100,000) and 51,000 died (17 per 100,000). There is some variation in incidence reported between different data sources and the true numbers are most likely an underestimate as they do not account for all of the settings where TBI may present, missed diagnoses and those who do not seek medical attention.

The vast majority of injuries, some 85% of those seeking treatment, are mild (Bazarian *et al.* 2005). Among those who are admitted to hospital, 20% have severe TBI's. The peak incidence by age is in the very young (0-4 years), adolescents (15-19 years) and older adults

(>75 years), with the most common causes of injury being falls (35%), road traffic accidents (17%) and assaults (10%). Across age groups, TBI rates are higher in men than women.

Risk factors for TBI include alcohol use and a past history of head injury. The latter has recently been investigated by Saunders and colleagues (2009) who reported that, of those admitted to hospital for a brain injury, 7% had at least one subsequent, recurrent brain injury during the follow-up period varying by subject between 2.5 to 7 years after their initial admission.

The definition of TBI varies between studies, including different descriptions of both concussion and mild traumatic brain injury (mTBI), making comparison between investigations difficult.

The most recent definitions include statements from the Veterans Affairs and Department of Defense (2009) and a Position Statement by the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health (Menon *et al.* 2010). The latter states:

"TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force."

Alteration in brain function is further defined as including one of any of the following clinical signs:

- Any period of loss or a decreased level of consciousness;
- Any loss of memory for events immediately before (retrograde amnesia) or after the injury (post-traumatic amnesia);
- Neurologic deficits (weakness, loss of balance, change in vision, dyspraxia, paresis/plegia [paralysis], sensory loss, aphasia, etc.);
- Any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.).

Other evidence of brain pathology is suggested to include visual, neuroradiologic or laboratory confirmation of damage to the brain and external forces are defined as including injury sustained from the head being struck by or striking an object; the brain being subject to acceleration/deceleration movements; a foreign body penetrating the brain and forces generated by a blast or explosion or other force yet to be defined.

The severity of TBI is most commonly indicated by the length of loss of consciousness and post-traumatic amnesia, i.e. the time between the trauma and the return of normal day-to-day memory. The Glasgow Coma Score (GCS) is most often used for assessing the level of consciousness in the acutely head injured but is a poor indicator of outcome, and does not differentiate well between those with mTBI. Table 1 summarises the different indices for TBI severity, adapted from Fleming (2008) and the Veterans Affairs and Department of Defense Guidelines (2009).

In terms of outcomes, injury severity measures are fairly poor indicators of prognosis. Roughly speaking, duration of post-traumatic amnesia (PTA) is the best indicator of neuropsychiatric outcome, and when longer than a month, is likely to result in reduced work capacity and if longer than three months, suggests voluntary work as the best outcome in terms of employment. PTA is more effective than GCS for predicting neurobehavioural outcomes at 6 months after injury (Tellier *et al.* 2009). There is a reasonable correlation between injury severity and developing cognitive impairment, personality and behavioural changes. Speed of information processing, memory and executive function are particularly affected.

	Mild	Moderate	Severe	Very Severe
GCS	13-15	9-12	6-8	3-5
LOC	≤ 30 mins	> 30 mins-6 hrs	>6 hrs-7 days	>7 days
PTA	≤ 24 hrs	> 24 hrs-14 days	> 14 days-8 weeks	> 8 weeks
AOC	A moment - 24 hrs	> 24hrs	-	-
Neuroimaging	Normal	Normal or abnormal	Normal or abnormal	Normal or abnormal

GCS - Glasgow Coma Score; LOC - Loss of Consciousness; PTA - Post-traumatic Amnesia; AOC - Alteration of Consciousness/Mental State

Table 1. After Fleming & Veterans Affairs and Department of Defense

3. Key pathology of Traumatic Brain Injury

In addition to clinical approaches to classification as already described, other classifications take account of the mechanism and pathology of the injury. Pathological changes are often also considered as primary and secondary, the latter including injury secondary to raised intracranial pressure, cerebral herniation, ischaemia, anoxia and cerebral oedema.

Closed brain injuries that involve impact with an object, result in acceleration and deceleration forces being transmitted to the brain and are associated with vascular injuries or haemorrhages, as well as diffuse axonal injury. Rotational injuries, with the head moving from side-to-side, are more likely to result in loss of consciousness than those that are associated with a nodding movement of the head (Smith & Meaney, 2000). Crush injuries by comparison, are less likely to be associated with loss of consciousness (Gonzalez Tortosa *et al.* 2004).

Inertial injuries do not require contact with another object, but result from the movement of the brain within the skull and are more commonly associated with diffuse axonal injury. Penetrating injuries, where the dura is breached, such as those seen from a knife or spike, result in local tissue necrosis and parenchymal damage resulting from the transit of the object through brain tissue. The injury associated with a gunshot wound is more widespread and often devastating as a result of the high-velocity forces involved.

Contusions or bruising of the surface of the brain arise from extreme localized forces such as those seen in an impact injury, for example a fall or assault. A contrecoup injury, i.e. a contusion on the opposite side of the injury, may be present. Certain areas of the brain are more vulnerable to contusions as a result of their close proximity to the bony skull. These include the medial-orbital surface of the frontal lobes and the temporal poles. In terms of the neuropsychiatric sequelae of brain injury, this is of little surprise, as these areas are most likely to affect social behaviour.

Diffuse Axonal Injury (DAI) results from the shearing rotational and linear forces exerted on axons as a result of acceleration and deceleration forces in impact or inertial injuries. The changes are predominantly seen in the parasagittal white matter, corpus callosum, brainstem long tracts and grey-white matter interface in the hemispheres. There are three degrees of DAI: Grade 1 reveals microscopic changes in the cortical white matter, corpus callosum, brain stem and cerebellum; Grade 2 is distinguished by isolated focal lesions in the corpus callosum and Grade 3 reveals additional focal lesions in the rostral brain stem.

Clinically, DAI may present with protracted periods of coma without evidence of intracerebral contusions.

Intracranial haemorrhage is classified by its location anatomically. There are four main subtypes: extradural, subdural, subarachnoid and intracerebral.

Extradural haemorrhages are most commonly seen overlying the convexity of the temporo-parietal region but can also be seen in around a third of cases overlying the frontal and occipital areas. Around 50% of extradurals are associated with a fracture of the squamous temporal bone resulting in damage to the underlying middle meningeal vessels.

Subdural haematomas are reported in around 5% of head injuries, increasing in incidence with injury severity. Acute subdurals, like extradural haemorrhages, have a mass effect and therefore, can produce secondary effects in brain injury. Chronic subdurals, often in association with alcohol use or a history of dementia, can follow a relatively mild or trivial head injury, although it is not always evident that there has been any trauma in up to 50% of cases. In those who fail to improve or present with a deteriorated mental state, a chronic subdural should be considered.

Cerebral oedema or brain swelling may arise acutely in the region of contusions and haematomas, is commonly cytotoxic and results in raised intracranial pressure, with the risk of cerebral herniation. The latter can involve extrusion of brain tissue under the falx, through the tentorium or more severely, the foramen magnum.

Oedema, haemorrhage, hypotension and poor respiratory ventilation can result in cerebral anoxia and this is a common finding after brain injury. Maintenance of arterial oxygen saturation and blood pressure are key to acute management in order to limit anoxia.

4. Neuroimaging after Traumatic Brain Injury

In the early stages of the acute presentation of head injury, investigation of brain injury neuropathology is aided considerably by the Computed Tomography (CT) scan (Coles, 2007). Images delineate extradural, subdural and intracerebral haematomas and any mass effect that they may exert, revealed through midline shift or compression of the midbrain cisterns. CT is used in preference to Magnetic Resonance Imaging (MRI) in acute management as it can be performed quickly and does not carry the risk of the magnetic field required in MRI that can move intracranial metallic objects or affect life support equipment (Gallagher *et al.* 2007). In one study, only 5% of those with severe brain injury have scans that are reported normal in all respects (Eisenberg & Levin, 1989). More recently, Bigler and colleagues (2006) have examined 240 consecutive brain injury rehabilitation admissions, identifying that the range of day-of-injury CT findings across injury severity is diverse and that severe injury can be associated with normal scans and mild injury with demonstrable CT lesions. This diversity of findings on CT, means that the utility of scans in predicting neurobehavioural outcomes is limited, at least when considered without other outcome measures.

In the subacute and chronic stages of their recovery, MRI is used in preference to CT to consider neuropsychiatric questions regarding patients with TBI. As contusions are predominantly at the bone-brain interface and subject to artefact and white matter changes that may be found after DAI are more easily detected, MRI is superior to CT in this setting. Generally speaking, T1 weighted images are best for gross brain anatomy; T2 images for cerebrospinal fluid (CSF) and CSF-related changes, as well as providing good contrasts between white and grey matter structures; gradient echo sequences detect blood by-products such as haemosiderin and fluid-attenuated inversion recovery (FLAIR) sequences provide

high quality visualization of white matter abnormalities. In those without other cerebrovascular or cardiac risk factors, the presence of haemosiderin is considered an indicator for DAI (Hahnel *et al.* 2008). Indeed, three times as many lesions were found on gradient echo in comparison to T2 images in those who sustained DAI in one study (Scheid *et al.* 2003).

Having said this, as MRI becomes more sensitive, it also reveals previously subtle or hidden abnormalities that may be incidental findings or unrelated to the brain injury. In particular, non-specific white matter hyperintensities can be found in healthy controls, with an increase in these findings with age. A normal gradient echo sequence some time after TBI equally does not imply the absence of previous bleeding. 20% of low-signal lesions consistent with haemosiderin deposits seen in the first year post-injury were no longer identified at two years in the study of Messori and colleagues (2003).

The relationship between clinical and neuroimaging findings on MRI has suggested some useful correlations. Jenkins and colleagues (1986) identified that the number of lesions and their location is related to degree and duration of consciousness. The deeper the lesions from the cortex, the more severe the injury. Levin and colleagues (1987) showed that there is a relationship between the size and location of frontal and temporal lobe lesions and deficits in neuropsychological assessment. Wilson and colleagues (1992) reported on the associations between MRI findings and outcome up to 18 months after injury. Neuropsychological outcomes correlated with MRI abnormalities, especially in deep brain regions, and ventricular enlargement correlated with persisting deficits at follow-up. Other changes that have been associated with clinical outcomes include atrophy of the corpus callosum and worse outcome in severe injury; slow information processing and generalized white matter atrophy; third ventricle enlargement and poor outcome. Hippocampal damage is a common finding in TBI where volume loss and temporal horn expansion indicate reduced structural integrity of the medial temporal lobe. The latter is useful for the psychiatrist in considering changes such as mood disorders or emotional lability, as well as abnormalities of memory. In those with a history of alcohol use, studies have suggested that atrophy may be greater after TBI, particularly in frontal grey matter (Jorge *et al.* 2005). Lesion location has been less readily associated with outcomes, although frontal lesions are associated with early agitation, aggression and behavioural problems.

Increasingly Diffusion Tensor Imaging (DTI) is being used to image white matter tracts and their connections after TBI and has been particularly useful in delineating the subtle changes in white matter pathways after mTBI (Singh *et al.* 2010; Lipton *et al.* 2009; Bazarian *et al.* 2007).

The electroencephalogram (EEG) can be useful in differentiating other causes of loss of consciousness besides head injury in the unconscious patient, but on the whole is of limited value in identifying outcome after brain injury. Indeed, a normal EEG can be associated with worse outcome in those whose symptoms persist after milder injuries. The EEG also cannot be relied on for identifying the risk of post-traumatic epilepsy with around 50% of brain-injured patients who do develop seizures having a normal EEG previously.

5. Common aetiological factors in neuropsychiatric presentations after Traumatic Brain Injury

Alongside injury severity, it is important to consider other factors in the aetiology of neuropsychiatric symptoms after brain injury. These factors are considered in more detail in the following discussion of specific disorders, although common features are considered here.

Preinjury constitutional factors found to have an impact on psychiatric outcome that have been investigated include socioeconomic status, psychiatric history, forensic history, alcohol misuse and length of education. The findings are, however, not consistent and other studies have failed to replicate convincing effects.

Premorbid personality traits are often noted in clinical assessment to be exaggerated or magnified after TBI, however the evidence for this is lacking in the literature (Tate 1998; Hall *et al.* 1998; Corrigan *et al.* 1998). Explanations for this apparent discrepancy include the retrospective assessment of premorbid personality being biased, poor measures of premorbid traits and the possibility that the clinically apparent effects in a few patients are too small to be replicated in the evaluation of large research cohorts.

More reliably, age at the time of injury is an important variable associated with increasing disability and cognitive impairment. Mortality rates increase (Kerr *et al.* 1971), physical comorbidity such as cerebrovascular disease becomes more prevalent and older patients have longer PTA regardless of injury severity (Katz & Alexander, 1994).

The psychological effects of the trauma are important and how patients feel as a result of their injury and its circumstances have been shown to have an impact on neuropsychiatric outcomes. The perception of fault has been shown to be important here, where those who blame a person or organization for their TBI are more likely to have psychiatric symptoms than those who perceive the injury as 'an Act of God' (Wood, 2004). However, it is also important to consider that the risk factors for violence overlap with important variables that may affect the psychiatric outcome of TBI such as alcohol use and socioeconomic class (Machamer *et al.* 2003).

Post-injury factors including environmental and social difficulties are also important in developing psychological sequelae. In particular, in those who have cognitive impairments, financial difficulties, occupational problems and threats to personal and family safety are considerably more difficult to cope with. Unstable domestic circumstances, a risky workplace or dangerous job, particularly when the accident occurred at work, can result in protracted disability. Changes in the family hierarchy and structure may be difficult to adjust to.

Ongoing personal injury claims and seeking compensation have been associated with prolonged disability. In a meta-analysis comparing 17 studies, symptom severity in those seeking compensation was worse by, on average, half a standard deviation than in those who were not. It was also suggested that the effect of compensation is greater for those with milder injuries (Binder & Rohling, 1996).

6. Long-term neuropsychiatric syndromes after Traumatic Brain Injury

6.1 Changes in personality

6.1.1 Prevalence

Clinicians have known for more than a century that TBI can result in significant changes in personality. The first widely recognized case was that of Phineas Gage, a 25-year old construction worker, who in 1848 survived an accident in which an iron rod entered through his left cheek, traversed the anterior portion of his brain and exited through the top of his skull (Lux, 2007). Whereas previously he was described as responsible, honest and capable, after the head injury he was childish and inconsiderate, with poor judgment (Reeves & Panguluri, 2011; Vaishnavi *et al.* 2009).

TBI can result in a variety of changes in personality and emotional regulation, from the most minor to striking. Preexisting personality traits can become more pronounced, or the personality can be drastically altered. The most frequent changes cannot easily be described by standard personality disorder classifications, although when such criteria are applied the most common categories identified are avoidant, borderline and paranoid (Hibbard *et al.* 2000; Koponen *et al.* 2002).

Pelegrin-Valero and colleagues (2001) evaluated 55 patients one year after severe TBI. The DSM IV criteria for personality change due to head injury were fulfilled in 60% of the patients and the most prevalent types were apathetic, unstable, disinhibited and aggressive. Apathy was the most prevalent symptom occurring in 34.5% of the sample. Kant and colleagues (1998) utilized the Apathy Evaluation Scale in a sample of 83 TBI survivors and found that apathy alone was present in 10.8% and apathy associated with depressive symptoms in up to 60%. Younger patients were more likely to be apathetic than older patients who were more likely to be depressed and apathetic.

6.1.2 Clinical presentation

The severity of the brain injury usually correlates reasonably well with the development of personality and behavioural changes. Common symptoms include apathy, loss of spontaneity and drive, labile mood, self-centred behaviour, disinhibition, irritability and reduced control over aggressive impulses. Personality changes are frequently associated with cognitive impairment and accompanied by a lack of insight and poor awareness of safety and personal hygiene. Symptoms of an altered personality can overlap with those of comorbid psychiatric problems, for instance those of a mood disorder (Fleminger, 2008).

Personality changes are one of the most distressing consequences of TBI for families and carers. In some instances spouses have described how their relationships have changed from one of equal partners to one more like that of a parent and child.

6.1.3 Aetiology

Personality changes may in some cases be attributed to the psychological reaction to the trauma. In others a discrete brain injury may cause isolated changes in social behaviour with little or no effect on neuropsychological testing (Fleminger, 2008).

During TBI the medial orbital surface of the frontal lobes and the anterior, inferior surface of the temporal lobes are particularly vulnerable to developing contusions. These regions play a major role in social behaviour with injury resulting in changes in personality.

Studies of patients acquiring open head trauma in war have demonstrated that frontal lobe injuries are in particular associated with personality changes. Feuchtwanger (1923) compared 200 patients with frontal wounds with 200 cases with injury to other parts of the skull. They found that those with frontal injury were more prone to exhibit euphoria, irritability, apathy and tactless, disinhibited behaviour. It has been suggested that convexity lesions over the lateral surface of the frontal lobe might produce a pseudodepressive clinical syndrome with apathy and indifference while medial and orbital frontal lesions produce a pseudopsychopathic syndrome with antisocial, tactless, impulsive and irritable behaviour.

Apathy has been associated with subcortical and right hemisphere injuries (Andersson *et al.* 1999). Cortico-striatal-pallidal-thalamic pathways, enclosing the anterior cingulate cortex, nucleus accumbens, ventral pallidum, and medial dorsal thalamic nucleus, are considered mediators of motivation and damage to these circuits can produce apathy. Dopamine is

associated with apathy, with dopaminergic antagonists increasing apathy, and agonists reducing it (Schwarzbold *et al.* 2008).

6.1.4 Treatment

Appropriate treatment includes providing emotional support and education for the patient and family members (Shawn *et al.* 2007; Vaishnavi *et al.* 2009). A cognitive behavioural approach to the symptoms may also be useful (Schwarzbold *et al.* 2008). Medication regimes should be simplified and drugs worsening the troublesome personality symptoms withdrawn. Pharmacological interventions, such as selective serotonin reuptake inhibitors (SSRI's) and mood stabilizers, can be used to target specific symptoms, including aggression and emotional instability (Shawn *et al.* 2007). Drugs improving motivation such as stimulants, activating antidepressants, dopaminergic agonists and cholinesterase inhibitors have been used in the treatment of apathy (Rao & Lyketsos, 2000). Co-morbid psychiatric disorders should be identified and treated as appropriate.

6.2 Cognitive disorders

6.2.1 Prevalence

Transient and persistent cognitive deficits are the most common complaints after TBI and are a major hindrance to recovery in areas of independent living, social re-adaptation, family life and vocational endeavors (McAllister, 2008). Cognitive impairment has been described at prevalence rates of 25-70% post-TBI (Vaishnavi *et al.* 2009).

6.2.2 Clinical presentation

Immediately after TBI, loss of consciousness or coma may ensue, followed by a variety of cognitive and behavioural abnormalities including agitation, confusion, disorientation, altered psychomotor activity and both retrograde and anterograde amnesia. This post-traumatic delirium can last from a few days to one month. Over the following 6-12 months cognitive function recovers to a variable extent, followed by a plateauing over the subsequent 12-24 months post-injury. In some cases permanent cognitive deficits result which typically include difficulties with attention, concentration, memory, language, executive functions and reduced speed of information processing (Rao & Lyketsos, 2000; Konrad *et al.* 2010). Long-term studies have shown that, in a proportion of patients, cognitive functions continue to improve or deteriorate for many years after the injury (Hammond *et al.* 2004; Millar *et al.* 2003). TBI may increase the risk of disinhibition in patients with dementia (Rao *et al.* 2010).

6.2.3 Aetiology

Cognitive deficits are caused by the cumulative effects of focal and diffuse brain damage. Focal injuries can cause corresponding impairments in selective functioning and the frontal and temporal lobes are particularly vulnerable to head injury. Clinical outcome depends upon the degree of diffuse injury, the presence and size of focal injury, the duration of LOC and PTA and clinical evidence of brain stem dysfunction at the time of injury (Rao & Lyketsos, 2000). The severity of the brain injury usually correlates reasonably well with the development of cognitive impairment (Fleminger, 2008).

The relationship between TBI and the development of dementia in later life remains a matter of debate. It has become clear that TBI can lead to a progressive neurodegeneration known

as chronic traumatic encephalopathy (dementia pugilistica / punch drunk syndrome) (Gavett *et al.* 2010). This may develop years after repeated head injury, especially in boxers. The fully developed syndrome includes cerebellar, pyramidal and extrapyramidal features, mixed cortical and subcortical cognitive deficits and a variety of behavioural manifestations. Chronic traumatic encephalopathy can produce cognitive symptoms alone or in conjunction with other neurodegenerative processes such as Alzheimer's disease (Gavett *et al.* 2010). The cytoskeletal lesions found in dementia pugilistica suggest strong pathogenetical relations with Alzheimer's disease (Jellinger, 2004).

Following a systematic review of 15 case control studies Fleming and colleagues (2003) found an association between a history of previous head injury and the risk of developing Alzheimer's disease (OR 1.58, 95% CI 1.21 to 2.06). This association was only found in males. This finding was supported by research following up head injured World War II veterans (Plassman *et al.* 2000). TBI may reduce the time to onset of Alzheimer's disease amongst those at risk of developing the disease (Nemetz *et al.* 1999).

Epidemiological studies and human autopsy data in small cohorts of patients with TBI and Alzheimer's disease indicate an increased risk of dementia after severe TBI compared with the general population (Jellinger, 2004). The accumulation of amyloid b peptide and tau pathology seen in Alzheimer's disease has been observed after experimental head trauma in animal models and demonstrated in some head injury patients who died several years after their injury.

The role of apolipoprotein E genotype for the prognosis of TBI and the later development of dementia is a matter of discussion. Although apolipoprotein Eε4 is suggested as a negative prognostic factor in TBI, with a possible neuroprotective effect of apolipoprotein Eε3, research studies have revealed variable results and convincing associations have not yet emerged (Verghese *et al.* 2011).

6.2.4 Treatment

Cognitive disorders are treated through a multidisciplinary approach focusing on neurorehabilitation. Specific cognitive deficits may improve through occupational therapy, physiotherapy, speech therapy, vocational training, cognitive rehabilitation and pharmacological interventions (Arciniegas *et al.* 2010).

TBI is associated with decreased dopaminergic activity and a hypocholinergic state (Writer & Schillerstrom, 2009). Agents increasing dopamine are reported to have positive effects on various domains of cognitive functioning. Methylphenidate has been shown to improve speed of cognitive processing and sustained attention (Neurobehavioural Guidelines Working Group, 2006; Shawn *et al.* 2007). It has been safely used in adults and children with TBI of all severities. Nonstimulant dopamine enhancers, including bromocriptine, amantadine, pramipexole and L-dopa, improve post-TBI cognitive impairments. Bromocriptine is recommended particularly for deficits in executive function, while amantadine is recommended for deficits of general cognitive function. Acetylcholinesterase inhibitors may help improve memory and attention.

6.3 Aggression

6.3.1 Prevalence

Post-TBI aggression is poorly defined and associated terms such as irritability, anger and agitation are often used in this context (Schwarzbold *et al.* 2008). As such it is difficult to

makes comparisons between studies and therefore to determine its true epidemiology. It has been suggested that post-traumatic agitation is a subtype of delirium, occurring during the period of post-traumatic amnesia, with specific behavioural and cognitive characteristics, whereas aggression indicates damaging, threatening or intimidating behaviour (Sandel & Mysiw, 1996).

Between 35 and 96% of post-TBI patients are reported to have exhibited agitated behaviour during the acute recovery period (Reeves & Panguluri, 2011). Although in many cases this behaviour resolves, it may also continue into the chronic phase and long term aggression is a common behavioural consequence of TBI (Fleminger, 2010). Tateno and colleagues (2003) studied 89 consecutive inpatients with moderate to severe TBI using the Overt Aggression Scale and found that 33.7% exhibited aggressive behaviour within the first six months of injury. 25% of TBI patients at six, 24 and 60 months post-discharge from an inpatient rehabilitation unit were still found to be displaying aggressive behaviour (Baguley *et al.* 2006). One large military study found that TBI increases the risk of discharge from military service for behavioural reasons four times compared with a non-TBI population (Hesdorffer *et al.* 2009).

6.3.2 Clinical presentation

Displays of aggression are somewhat varied among patients with TBI but are often consistent for an individual patient (Reeves & Panguluri, 2011). Aggression is usually impulsive, out of proportion to the stimulus and short lived (known as Episodic Dyscontrol Syndrome). Anger and impulsive verbal outbursts seem to be the main characteristics of aggression post-TBI (Dyer *et al.* 2006). Aggression is associated with the presence of major depression and is also more frequently encountered in post-TBI mania (Kim, 2006; Tateno *et al.* 2003). post-TBI aggression can pose a serious challenge to long term rehabilitation and is a major cause of disability to individuals and a source of stress to their families (Wood & Liossi, 2006).

6.3.3 Aetiology

Emotion is normally regulated in the human brain through a complex circuit consisting of the orbital frontal cortex, amygdala, anterior cingulate cortex, and several other interconnected regions (Davidson *et al.* 2000). It is hypothesized that damage to the prefrontal cortex affects its regulatory role in controlling behaviour resulting in a loss of self-control with spontaneous aggressive and violent behaviours (Grafman *et al.* 1996). Studies on Vietnamese War veterans have shown an association between frontal ventromedial lesions and higher aggressive/violent behaviours. Serotonin is the most widely studied neurotransmitter in aggressive behaviour and the prefrontal cortex receives a major serotonergic projection which is dysfunctional in individuals who show impulsive violence. Other risk factors for post-TBI aggression include a history of antisocial behaviour, arrest, poor premorbid functioning and substance misuse (Greve *et al.* 2001; Kolakowsky-Hayner & Kreutzer, 2001; Tateno *et al.* 2003). There is inconsistent evidence relating the impact of socioeconomic status and severity of the injury to the development of post-traumatic aggression (Kim *et al.* 2007).

6.3.4 Treatment

Environmental interventions rather than drug therapies are often the preferred means of managing agitation in the acute post-TBI phase (Fleminger *et al.* 2006). However, in the

absence of response to behavioural and environmental modification, and in the later stages of recovery, pharmacology is frequently used (Lombard & Zafonte, 2005). There is limited evidence regarding the most effective drug treatment for aggression post-TBI. Randomised controlled trials have demonstrated the effectiveness of beta-blockers such as propranolol and pindolol. Anticonvulsants such as carbamazepine and valproate have been reported to be effective in clinical practice. Atypical antipsychotics, antidepressants, buspirone, lithium and amantadine have also been used to manage post-traumatic aggression.

6.4 Mood disorders

6.4.1 Depression

6.4.1.1 Prevalence

Depression is recognized as a common complication of TBI but estimations of its frequency vary¹³. Prevalence rates for major depressive disorder have been described between 15 to 61% (Kim *et al.* 2007; Jorge *et al.* 2004). This high variability in findings is largely due to differences in methodology for defining and measuring depression.

An association has been identified between a history of TBI and an increased lifetime prevalence of major depression. Holsinger and colleagues (2002) found that the lifetime prevalence of major depression among men who sustained a head injury during World War II was 18.5% compared to 13.4% in those without a head injury.

6.4.1.2 Clinical presentation

Diagnosing depression is complicated because the cognitive, emotional and somatic symptoms of depression can overlap with direct symptoms of TBI. For example, sleep disturbance, concentration difficulties and apathy are common symptoms in TBI survivors both with and without mood disorders. The symptoms of post-TBI depression do not differ from those with depression without associated head injury although they are more frequently characterized by irritability, anger and aggression than by sadness (Reeves & Panguluri, 2011). Psychiatric comorbidity is common in patients with depression after TBI.

Studies have shown an association between TBI and suicidality. In a retrospective study of 5,034 patients Silver and colleagues (2001) reported that patients with a history of TBI were four times more likely to attempt suicide than those without previous head injury. This risk remained even after they controlled for demographics, quality of life variables, alcohol abuse and comorbid psychiatric disorders. A study of suicidality after TBI found that 35% of individuals had clinically significant levels of hopelessness, 23% had suicidal ideation and 17% had attempted suicide in the five years since their injury (Dilley & Fleminger, 2006).

6.4.1.3 Aetiology

Risk factors for the development of post-TBI depression include stress, social isolation and maladaptive coping styles, suggesting that personal reactions to TBI deficits influence depressive symptomatology. Jorge and colleagues (2004) identified that patients with TBI with major depression were more likely to have a personal history of mood and anxiety disorders than patients who did not have major depression. No relationship was identified between development of post-TBI depression and with head injury associated loss of consciousness, skull fracture or accompanying physical and cognitive impairments (Malaspina *et al.* 2001).

Depression may be seen after TBI of any severity, but the correlation between head injury severity and the degree of depression is controversial, with studies giving conflicting results. However, a moderately strong association has been found between patient self-assessment of post-TBI ability and depression (Malec *et al.* 2010). Psychosocial factors have a major impact on depression rates at longer post-injury intervals whereas early post-traumatic depression may be more strongly related to a host-injury interaction (Jorge *et al.* 1993a; Silver *et al.* 2009).

Investigations determining the relationship between specific regional brain injury and depressive symptoms have proven inconsistent. Studies have shown an association between post-TBI depression and lesions in the left dorsolateral prefrontal cortex and left basal ganglia in the acute phase of TBI (Fedoroff *et al.* 1992). Jorge and colleagues (2004) found a reduction in the left prefrontal grey matter volume on MRI scanning, especially in the ventrolateral and dorsolateral regions, in patients with post-TBI depression. Lateral frontal lesion locations are associated with an increased risk of developing depression compared to medial lesions, with right lateral lesions increasing the risk of anxious depression and left anterior lesions increasing the risk of major depression (Paradiso *et al.* 1999; Jorge *et al.* 1993b).

It has been proposed that damage to the neural circuits involving the prefrontal cortex, amygdala, hippocampus, basal ganglia and thalamus may be related to the development of depression after TBI. During trauma diffuse axonal damage is common in the frontal and anterior temporal lobes providing an explanation for the high rate of mood disorders in this group. Rupture of the biogenic amine containing neurons, as they pass through the basal ganglia or frontal-subcortical white matter, may be related to the development of depression due to TBI.

Saran (1985) found that depression after minor closed head injury was not correlated to abnormal dexamethasone suppression test results, suggesting that depression post-TBI is not associated with hypothalamic pituitary adrenal axis dysfunction. However this study was limited by its small sample size.

Disruption in hippocampal functioning and morphology has been described in cognitive and depressive disorders (Campbell & Macqueen, 2004). Jorge and colleagues (2007) measured hippocampal volume through MRI in a sample of 37 TBI survivors and found lower bilateral hippocampal volume and reduced left frontal grey matter in patients who developed depression.

6.4.1.4 Treatment

The treatment of post-TBI depression is similar to that of depression in primary psychiatric practice and includes psychological interventions, antidepressants and ECT. SSRI's are considered first line as they are usually safe and well tolerated (Fann *et al.* 2009). Tricyclic antidepressants have a lesser role both because of the higher incidence of anticholinergic side effects that can adversely affect cognition and due to evidence of possible reduced efficacy. MAOI's are not recommended due to lack of efficacy data and potentially serious side effects, particularly when dietary restrictions are not adhered to in a population with a high rate of cognitive difficulties. All antidepressant drugs lower the threshold for seizures, which is a particular concern in TBI patients, but it must be remembered that a lower threshold does not necessarily imply increased seizure frequency (Turner-Stokes & MacWalter, 2005). ECT appears a viable option for treatment in refractory patients. Psychotherapy, in particular CBT, can also be used if the patient's cognitive status does not preclude it.

6.4.2 Mania

6.4.2.1 Prevalence

There is evidence that TBI is a risk factor for bipolar disorder (Mortensen *et al.* 2003). Both unipolar mania and bipolar disorder have been observed after TBI. However, studies are rare and often hampered by small sample sizes. These disorders do not present a problem of the same degree of magnitude as that presented by post-TBI depression (Lux, 2007).

Mortensen and colleagues (2003) found that head injury is a risk factor for bipolar disorder and that TBI survivors are 1.5 times more likely to develop this than those without TBI. Van Reekum and colleagues (2000) reviewed the literature and found a prevalence of 4.2% for mania probably caused directly by TBI. There is evidence that secondary mania is more prevalent in males.

6.4.2.2 Clinical presentation

It is difficult to differentiate between mania directly attributable to TBI and mania simply observed following TBI. Likely indicators include a close temporal association in the absence of other aetiological factors (such as a lack of previous psychiatric history or negative family history) and atypical presentations such as unusual age of onset (Schwazbold *et al.* 2008).

Diagnosis can additionally be complicated as symptoms of mania can be confused with changes in personality associated with frontal lobe syndrome, such as tactless, impulsive and irritable behaviour. Mania due to TBI may present with more aggression, irritability and less euphoria (Shukla *et al.* 1987).

6.4.2.3 Aetiology

It has been suggested that a correlation exists between the severity of the TBI and severity of post-TBI mania. Hypomania and bipolar II disorder have been associated with milder trauma (briefer durations of post-traumatic amnesia), whereas chronic hypomania, bipolar I and schizoaffective disorder were associated with more severe trauma. However, these results have not been consistently replicated. Jorge and colleagues (1993) found that post-traumatic mania was not associated with the severity of brain injury, degree of physical or cognitive impairment, level of social functioning or previous family or personal history of psychiatric disorder. Robinson and colleagues identified an association between secondary mania and a family history of affective disorder (Robinson *et al.* 1988).

An association has been shown between post-TBI mania and multifocal brain lesions, primarily in temporal basal poles (Jorge *et al.* 1993b). Starkstein and colleagues (1987) suggested that the confluence of either anterior subcortical atrophy and a focal lesion of a limbic or limbic-connected region of the right hemisphere, or a genetic predisposition and a limbic-connected right hemisphere lesion may account for the necessary factors to produce secondary mania.

6.4.2.4 Treatment

There is limited evidence in the literature about specific treatments for mania post-TBI. Mood-stabilizing antiepileptic drugs have proved effective, in particular valproate and carbamazepine (Shawn *et al.* 2007). Atypical antipsychotics are another treatment option, especially in patients who have manic symptoms accompanied by psychotic features. Lithium carbonate should be avoided as it lowers the seizure threshold, may worsen cognitive impairment and has a low therapeutic index.

6.5 Anxiety disorders (including Post Traumatic Stress Disorder)

6.5.1 Prevalence

Anxiety disorders are common after TBI and have been reported at rates as high as 70% (Moore *et al.* 2006). All variants are seen including GAD, panic disorder, phobic disorders, PTSD and OCD. Research indicates that the prevalence rates of anxiety disorders amongst patients with TBI are: 3-28% for GAD, 4-17% for panic disorder, 1-10% for phobic disorders, 2-15% for OCD and 3-27% for PTSD. Anxiety disorders are frequently comorbid and are also associated with depression.

6.5.2 Clinical presentation

The most frequently studied anxiety disorder associated with TBI is PTSD. This is characterized by the re-experiencing of the traumatic event through nightmares and intrusive thoughts, associated with symptoms of hyperarousal and avoidance behaviours. The possibility that PTSD can develop following TBI has been an area of controversy and debate, with some authors considering mild TBI and PTSD mutually exclusive (Sbordone & Liter, 1995). The traditional view held that impaired consciousness, typically associated with TBI, precludes encoding the traumatic experience and that this prevents subsequent re-experiencing symptoms (Bryant, 2001; Sbordone & Liter, 1995). However, research has increasingly indicated that PTSD may manifest even when memories of the incident are limited by loss of consciousness (Greenspan *et al.* 2006). In these cases flashbacks are either absent or their content is thematically related to the trauma sustained.

6.5.3 Aetiology

Research has not produced consistent findings with regards to identification of specific brain lesions in the development of PTSD after TBI. Sojka and colleagues (2006) investigated serum levels of cortisol (a biochemical marker of stress), S-100B and neuron-specific enolase (two biochemical markers of brain tissue injury) in the acute phase in mild traumatic brain injury patients and in the occurrence of post-traumatic stress-related symptoms one year after the trauma. There was a positive correlation between the levels of S-100B in the TBI acute phase and the presence of PTSD one year later. This may reflect the complexity of interactions between brain tissue injury and the ensemble of stress reactions.

Many of the studies examining the relationship between PTSD and TBI have focused on the association between post-traumatic amnesia and PTSD. Bryant has suggested that patients amnesic for the trauma can re-experience vivid pseudomemories of the event generated through a combination of imagination and information learnt following the trauma (Bryant, 1996). There is evidence that memories can be encoded outside of awareness and these memories can influence ongoing emotions and behaviours. Therefore, it is possible that in PTSD some of the traumatic event is coded even during the periods of consciousness disturbances. Subsequently, exposure to similar situations could reactivate these memories. King (1997) has proposed that patients may re-experience fragments (or islands) of memory preserved within the amnesic period. Alternatively, Bryant and colleagues (2004) have shown an association between higher heart rates in the TBI acute phase and subsequent development of PTSD and hypothesized that fear conditioning occurring outside the level of awareness could contribute to PTSD development.

Acute stress disorder has been shown to be a reasonable predictor for the subsequent development of PTSD (Harvey & Bryant, 2000). Avoidant coping style, behavioural coping

style (versus a cognitive coping style), and a history of prior unemployment (an indicator of the premorbid level of functioning) are predictors of PTSD severity (Bryant *et al.* 2000). In addition the severity of PTSD symptoms is also associated with external attributions to others of causality for the event (Williams *et al.* 2002).

Gil and colleagues (2005) followed a cohort of 120 subjects for six months after mild TBI and found that memory of a traumatic event within the first 24 hours is a strong predictor and a potential risk factor for subsequent development of PTSD (Gil *et al.* 2005). Turnbull and colleagues showed that although amnesia for the traumatic event did not protect against PTSD it did protect against the severity of symptoms and was specifically protective against intrusive symptoms (Turnbull *et al.* 2001). Longer post-traumatic amnesia appears to be protective against selected re-experiencing symptoms and patients unconscious during the trauma may have less re-experiencing symptoms (Bryant *et al.* 2009; Glaesser *et al.* 2004).

6.5.4 Treatment

Limited data exists regarding the effectiveness of psychopharmacological agents for the treatment of anxiety disorders in patients with TBI. However, case reports support the use of SSRI's and venlafaxine. Buspirone is another reasonable treatment option.

Benzodiazepines and antipsychotics should largely be avoided as they cause memory impairment, disinhibition and delayed neuronal recovery. If benzodiazepines are required in the short term, cautious dosing with longer acting agents such as clonazepam is recommended.

Cognitive behavioural therapy, neurorehabilitation and psychotherapy are important in treatment (Soo & Tate, 2007).

6.6 Mild Traumatic Brain Injury and Postconcussional Syndrome

6.6.1 Prevalence

Mild Traumatic Brain Injury (mTBI) is classically defined as an essentially reversible syndrome without detectable pathology. Around 80% of all TBI's are mild and 15% are associated with persisting symptoms. Postconcussional syndrome (PCS) is poorly defined, but is generally understood to refer to those who have persisting symptoms. PCS has been a source of controversy for many years. Understanding the true scale and scope of the problem has been complicated by lack of specificity of symptoms, disagreement between diagnostic systems on key criteria and lack of clarity over pathogenesis (Williams *et al.* 2010). PCS can occur with head injury of any severity but more often follows mTBI.

6.6.2 Clinical presentation

The immediate symptoms of mTBI include headache, nausea, dizziness, unsteady gait, slurred speech, poor concentration and slowness in answering questions. Speed of recovery is variable but reports of those who have sustained sports injuries reveal a rapid resolution, with the majority being free of symptoms at two weeks. At six weeks, emotional symptoms such as irritability and anxiety may predominate over more physical and cognitive features. Headaches are more commonly reported at follow-up.

Although the duration and severity of mTBI symptoms are highly variable amongst individuals, they are usually self-limiting and permanent cognitive, psychological or psychosocial problems are uncommon (Iverson, 2005). Belanger and Vanderploeg (2005) carried out a meta-analysis of the literature to determine the impact of TBI sports-related

concussion. They reported that the acute effects of concussion were greatest on global measures of cognitive functioning and memory. No residual neuropsychological impairments were found beyond seven days post-injury. Most patients with TBI will have fully recovered three to six months post-injury but 15% will have symptoms lasting longer than 1 year (Rutherford *et al.* 1979).

PCS refers to a cluster of somatic, mood and cognitive symptoms that persist for weeks, months or even years. These include headache, dizziness, memory loss, problems with concentration and attention, irritability, hyperactivity, sleep disturbance and emotional lability. Loss of consciousness is not necessary for its development. These symptoms are not specific to PCS and can occur in both TBI and non-brain injured patients (Meares *et al.* 2011). Overlap of PCS symptoms with other populations is marked, including individuals with depression, chronic fatigue, whiplash and pain.

6.6.3 Aetiology

There is much debate over whether the symptoms of PCS are neurologically or psychologically driven and how premorbid factors may influence the presentation. Current evidence supports the hypothesis that in the early phases of the syndrome neurological factors play a greater role but that over time psychological issues appear to become particularly relevant.

The physiological changes following mTBI at the cellular level have been extensively examined through animal and *in-vitro* modeling. From a neurological perspective it is assumed that most of the pathophysiology of concussion occurs following acceleration and deceleration forces which render neurons and neural systems dysfunctional but not destroyed.

At the time of the TBI, in the majority of cases, neurological examination and testing reveal either no abnormalities or minimal deficits. However, there is emerging evidence in certain cases linking neurocognitive dysfunction to neuroimaging findings post-TBI (Williams *et al.* 2010). Subsets of patients with presumed PCS have been shown to have abnormalities on positron emission tomography (PET) and single-photon emission computed tomography (SPECT) (Chen *et al.* 2003; Abu-Judeh *et al.* 1999). Functional imaging studies (fMRI) have indicated differential patterns of activity on working memory tasks following concussion (McAllister *et al.* 2001).

There are elevated rates of psychiatric comorbidity in patients with PCS. This may represent a response to persisting effects of brain injury on cognition and associated limitations in functioning. Alternatively, patients with chronic fatigue syndrome, chronic pain, depression or PTSD are likely to exhibit many post-concussion-like symptoms making misdiagnosis easy. Patients who experience mTBI complicated by depression report more post-concussional symptoms and more severe symptoms than patients with head injury without depression (Lange *et al.* 2011). Patients with symptoms of depression, anxiety and PTSD at seven to ten days post-mild-TBI predict post-concussional symptoms three to six months later. Symptom reporting is believed to be associated with premorbid personality characteristics and patients' negative perceptions of their illness early after head injury plays a role in the persistence of post-concussional symptoms (Whittaker *et al.* 2007). It has been suggested that in some patients with long-standing post-concussional symptoms, the extent and severity of the symptoms suggest that the illness is a form of somatization disorder (Fleminger, 2010).

Risk factors for development of PCS include female gender, previous psychiatric history and previous head injury (Meares *et al.* 2008). There remains a consistent association with involvement in medicolegal action and poorer outcomes (Belanger *et al.* 2005).

6.6.4 Treatment

Early educational information about PCS has been shown to be effective in reducing the number and severity of symptoms in the initial weeks (Borg *et al.* 2004). Longer term psychotherapy, occupational and vocational intervention and social skills training are used as necessary. A recent systematic review of psychological approaches to PCS identified that CBT may be effective (Sayegh *et al.* 2010) and an, as yet unpublished, randomized controlled trial of cognitive therapy has also shown a positive outcome from this intervention (Fleminger & Potter, personal correspondence).

6.7 Psychosis

6.7.1 Prevalence

Definitions of post-traumatic psychosis vary considerably in the literature with corresponding wide ranges of prevalence rates described. Transient psychotic symptoms are not uncommon after head injury, especially during a period of delirium immediately after TBI. Psychotic symptoms can occur as a complication of post-traumatic epilepsy, in the context of TBI related mood disorders or associated with a clinically problematic chronic schizophrenia-like condition.

The association between TBI and schizophrenia remains a subject of debate and controversy. Davidson and Bagley (1969) concluded that between 0.07% and 9.8% of patients with TBI develop a post-traumatic schizophrenia-like psychosis, with prevalence rates increasing over time. The authors concluded that TBI increases the prevalence of schizophrenia by two to threefold over 10-20 years. Most of these patients did not have a family history of schizophrenia. Van Reekum and colleagues (2000) reviewed data from more recent studies and found a prevalence of post-traumatic schizophrenia of 0.7%. Men appear to be more frequently affected by post-head injury psychosis than women (Fujii *et al.* 2002).

David and Prince (2005) appraised the literature to identify a causal role of TBI in schizophrenia and concluded that the evidence for such an association does not exist. They suggest that any association may be the result of reverse causality. It is clear that large scale epidemiological studies are needed to determine if head injury can be considered to be causally implicated as a risk factor for schizophrenia.

6.7.2 Clinical presentation

Psychotic features can be transient or persistent and may follow either an acute or chronic course. Following head injury the clinical features of delirium include confusion, inattention, cerebral disorganization and psychotic symptoms incorporated into this context. When the patient emerges from delirium, more discrete psychotic features might become evident and characteristic symptoms include delusional disorientation, delusional misidentification and confabulation. Confabulations may become chronic, especially in the context of associated global cognitive impairment and lack of insight.

The longer term clinical presentation has considerable overlap with primary schizophrenic disorder, with a prominence of persecutory and other delusions and auditory hallucinations. The onset is often gradual, with a subacute or chronic course (Zhang &

Sachdev, 2003). Prodromal symptoms are common and they include depression, antisocial and inappropriate social behaviour, social withdrawal and deterioration at work. Negative and catatonic features are unusual (Sachdev *et al.* 2001; Fujii & Ahmed, 2002).

Sachdev and colleagues (2001) reported a mean latency of 54.7 months between head injury and onset of psychosis, with the minimum being two weeks and the maximum 17 years. This study also noted a mean age of onset of 26.3 years.

6.7.3 Aetiology

Establishing a direct causal association between TBI and psychosis is difficult and consequentially differentiating patients with psychosis attributable to TBI from patients with primary psychosis who have suffered a head injury in the past is complicated. A genetic predisposition to schizophrenia may be a vulnerability factor for TBI psychosis. However schizophrenia commonly presents in men in their late teens / early 20's and this population are also at a high risk for suffering a head injury. TBI might be more common in families with a proband with schizophrenia and the trauma might increase the risk of manifesting the disorder.

Patients with psychosis secondary to TBI are more likely to have had a previous congenital neurological disorder or to have sustained a head injury prior to adolescence than TBI patients without psychosis (Fujii *et al.* 2001). Reports vary with regards to the severity of TBI required to trigger a psychosis. Some studies suggest that individuals who develop a psychosis after TBI had generally sustained moderate to severe head injuries. This contrasts with case studies reporting the development of a psychosis after mild brain injuries with no loss of consciousness.

Patients with psychosis following TBI have demonstrated more impairment on neuropsychological testing compared to those with TBI but without psychosis. Specific cognitive areas included deficits in general intelligence, verbal memory, executive functioning and vocabulary. The first three deficits are similar to those found in schizophrenic patients (Fujii *et al.* 2004).

Smeltzer and colleagues (1994) reviewed the evidence related to an anatomical localization of brain injury and relationship to psychosis. They found the evidence to be sparse, inconsistent and flawed. Some studies suggest that psychosis is related to left sided and temporal injuries but others find no relationship to the type or location of the injury.

Fujii and Ahmed (2002) analysed data from 69 published case studies of psychotic disorder due to TBI in order to describe common characteristics. They found abnormalities on EEGs in 70% of cases, especially within the temporal lobes and almost 30% had seizures. About 65% of the cases reported positive findings on MRI/CT which included focal lesions and atrophy in equal quantities and the most common location of findings was in the frontal lobes. These findings occurred in equal occurrence in the left and right hemispheres.

6.7.4 Treatment

Treatment with typical antipsychotics may cause a functional decline in patients with TBI who already have diminished dopaminergic circuits as a result of frontal brain injury. Therefore atypical agents, with less dopamine antagonism and greater serotonergic properties are preferred. Atypical antipsychotics, particularly olanzapine, are considered to be first line treatment of TBI psychosis. Initial doses should start low, at one third to one half

the usual starting dose, as individuals are particularly susceptible to side effects. The full range of psychotropic medication side effects are seen in individuals with TBI. Clozapine can lower the seizure threshold, which can be problematic in TBI, and also has anticholinergic properties that can further impair cognitive function and may provoke delirium.

7. Summary of pharmacological treatment guidelines

The evidence for pharmacological and psychological treatment strategies for neuropsychiatric disorders is limited, as has been discussed. Two recent reviews of pharmacological management have identified the best evidence available, targets for future research and attempted to recommend best practice guidelines. Reference to these reviews is recommended (Warden *et al.* 2006; Chew & Zafonte, 2009).

Careful neuropsychiatric assessment needs to precede the development of the treatment plan. Making sure that the diagnosis is correct, that treatment is being taken and whether the dose of treatment is effective or has been given for an adequate trial period all need to be considered. When reviewing medications, it is important to ask oneself repeatedly what the drug is being given for and where there is no effect or benefit, stop it.

Practically speaking, when managing the neuropsychiatric sequelae of brain injury there are a number of principles that should be borne in mind. Wherever possible, the psychiatrist should wait to see how symptoms evolve and whether they remit spontaneously. Drug treatments should be started at lower doses and gradually titrated, avoiding polypharmacy wherever possible. Particular care about drug-drug interactions, and particularly interactions with antiepileptics and warfarin, should be taken. The iatrogenic effects of some agents in worsening cognitive impairment, for example through anticholinergic effects or causing akathisia and worsened agitation, should be taken into account when choosing appropriate agents.

The following treatments are recommended in the clinical management of neuropsychiatric disorders with the caveat that further research is required to ascertain effectiveness in the brain injured patient:

Long-term Aggression: Valproate or Carbamazepine or Sertraline

Cognitive Dysfunction: (Impaired Attention) Methylphenidate or Cholinesterase Inhibitors; (Memory) Cholinesterase Inhibitors; (Executive Dysfunction) Bromocriptine

Depression and Anxiety: Sertraline

Mania: Valproate or Carbamazepine or Olanzapine

Psychosis: Olanzapine

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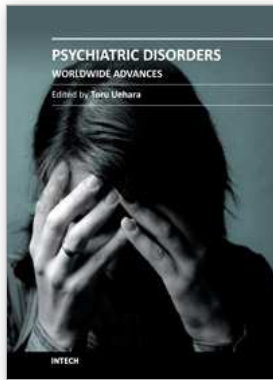
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A psychiatric disorder is defined as any complex condition that involves the impairment of cognitive, emotional, or behavioral functioning. Aside from knowing the physical organic factors, its causal pathology has remained a mystery. Regarding recent advances in psychiatry and neurosciences, psychiatric disorders have been closely associated with socio-cultural, psychological, biochemical, epigenetic or neural-networking factors. A need for diverse approaches or support strategies is present, which should serve as common knowledge, empathetic views or useful skills for specialists in the field. This book contains multifarious and powerful papers from all over the world, addressing themes such as the neurosciences, psychosocial interventions, medical factors, possible vulnerability and traumatic events. Doubtlessly, this book will be fruitful for future development and collaboration in "world psychiatry".

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