

Neuropsychiatric Sequelae of Traumatic Brain Injury

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The authors review the psychiatric disturbances associated with traumatic brain injury. They highlight the close link between traumatic brain injury and psychiatry and provide an overview of the epidemiology, risk factors, classification, and mechanisms of traumatic brain injury. They describe various neuropsychiatric sequelae, and the respective treatments are outlined with emphasis on a multidisciplinary approach. (Psychosomatics 2000; 41:95–103)

[Note: The following article is the fifth in a special neuropsychiatry series edited by Dr. Constantine Lyketsos. The first four articles appeared in the January–February 2000 issue of Psychosomatics.]

Trauma is a common cause of brain injury in the United States and is a significant public health problem.¹ Traumatic brain injury (TBI) can result in a variety of neuropsychiatric disturbances ranging from subtle deficits to severe intellectual and emotional disturbances. In rare cases, it results in chronic vegetative states. The neuropsychiatric disturbances associated with TBI include cognitive impairments, mood disorders, anxiety disorder, psychosis, and behavioral problems.

This article will provide an overview of the common neuropsychiatric sequelae of TBI along with a guide to the assessment and treatment of these conditions. The primary goal of this review is to demonstrate the link between psychiatry and TBI. We will summarize the epidemiology, risk factors, classification, and mechanism of brain injury after TBI. Next, a description of the various neuropsychiatric disorders associated with TBI will be provided. Finally, a brief discussion of pharmacological treatment in TBI will be outlined, followed by concluding remarks.

GENERAL OVERVIEW OF TBI

Epidemiology

The annual incidence of head trauma in the United States is approximately 2 million per year.¹ Of these patients,

500,000 will probably require hospitalization, and about 80,000 will suffer from some level of chronic disability.¹ Men are injured twice as frequently as women, with the risk of fatal head injury being four times greater. The incidence of head injury increases to peak from ages 15 to 25, thereafter falling off, only to rise again in later years.² In persons under 45 years of age, TBI is the leading cause of death and disability, with an overall mortality rate of 25 per 100,000. Motor vehicle accidents are the most common cause of head injury, accounting for more than 50%, followed by falls (21%), violence (12%), and injuries from sports or recreational activities (10%).³ Health costs from TBI are estimated to be on the order of \$35 billion per year.⁴

Risk Factors for Neuropsychiatric Disorders

The major risk factors for neuropsychiatric disturbances after TBI include increasing age, arteriosclerosis, and alcoholism. These all delay the reparative process within the central nervous system.⁵ Premorbid personality also plays a significant role in the process of rehabilitation, as was pointed out by Symonds: “The response to head injury depends on the kind of head that was injured.”⁶

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Similarly, factors such as marital discord, poor interpersonal relationships, problems at work, or financial instability are important contributors to the neuropsychiatric disability.^{7,8}

Classification of Head Injury

Head injury can be classified along several lines. The most common classification is based on physical trauma: open vs. closed head injury, depending on whether or not the skull has been breached.

Another important classification system depends on the severity of initial impairment, combining the initial Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC), and the duration of posttraumatic amnesia (PTA).⁹ A GCS of 13–15, LOC of less than 30 minutes, and/or PTA of less than 1 hour is classified as mild TBI. People with moderate TBI have a GCS of 9–12, LOC of 1–24 hours, and/or PTA of 30 minutes to 24 hours. A GCS of 8 or less, LOC of more than 24 hours, and/or PTA of more than 1 day is classified as severe TBI.⁹ Some studies have used only the GCS to classify the severity,¹⁰ whereas others have used LOC and/or PTA.¹¹ The prognosis of moderate and severe TBI is fairly well correlated with these characteristics, but the relationship is not as clear with milder forms of TBI, which falls into a less well-defined spectrum.

Mechanisms of TBI

TBI is the result of mechanical forces applied to the skull and transmitted to the brain. This may lead to focal and/or diffuse brain damage. Focal lesions often result from a direct blow to the head and include brain laceration, contusion, intracerebral hemorrhage, subarachnoid or subdural hemorrhage, and ischemic infarct. Contusion occurs directly beneath or contralateral to the site of impact, commonly referred to as *coup* and *contre-coup* injury.¹² It is most common in the orbital–frontal area and the temporal tips, where acceleration/deceleration forces cause the brain to impact on the bony protuberances of the skull.¹³

Diffuse brain injury also results from the differential motion of the brain within the skull, causing a shearing and stretching of the axons.³ This can produce a wide spectrum of injuries, ranging from brief physiological disruption to widespread axonal tearing, called diffuse axonal injury (DAI).¹⁴ In addition to brain damage occurring at the time of the impact, secondary damage from several processes may occur during the recovery period. These include hyp-

oxia, anemia, metabolic abnormalities, hydrocephalus, intracranial hypertension, fat embolism, and subarachnoid hemorrhage. Other delayed effects include release of excitatory amino acids, oxidative free-radical production, release of arachidonic acid metabolites, and disruption of neurotransmitters like monoamines and serotonin.^{15–17}

NEUROPSYCHIATRIC SEQUELAE OF TBI

The neuropsychiatric disturbances associated with TBI are numerous. They are generally observed to be disorders of mood, cognition, or behavior. Cognitive deficit has been variously classified as delirium,¹⁴ dementia due to head trauma,² amnesic disorder due to head trauma,² or intellectual impairment,¹⁸ depending on the variety of symptoms and their time of onset and resolution. The behavioral problems associated with TBI have been the most difficult to classify. The signs and symptoms of the frontal and temporal lobe damage have been variously classified as frontal and temporal lobe syndromes,⁹ aggressive disorders,¹⁹ and personality changes.^{2,14,18}

In our opinion, these terms are too restrictive to describe the complex clinical manifestations of diffuse brain damage. Organic Personality Syndrome or Personality Changes Due to Head Trauma are also misnomers, as there are no prospective studies to document that these symptoms are an exaggeration of premorbid personality. The DSM-IV classification of the neuropsychiatric sequelae of TBI is also inadequate. Except for “dementia due to head trauma,” all other disorders are classified as “disorder due to general-medical condition.” The term *post-concussion syndrome* (PCS), frequently noted in the literature, is also vague and nondescriptive. It is also a misnomer because it can be seen in anyone with TBI, with or without a “concussion.”

We propose a classification of the neuropsychiatric sequelae of TBI according to their phenomenology as described in Table 1. We prefer the term “behavioral dyscontrol disorder, major variant” to describe a specific syndrome of mood, cognitive, and behavioral disturbances following head injury. The term “behavioral dyscontrol disorder, minor variant” is preferred to describe what is known as “post-concussion syndrome.” We believe that both these disorders have the same etiopathogenesis; that is, diffuse brain damage, with predominance of frontal and temporal lobe lesions, as they are more likely to be injured. The two disorders probably differ only in the severity of their symptoms—major variant being more severe. The major variant has predominantly behavior symptoms, com-

pared with the minor variant, which has more somatic symptoms. What follows is a discussion of these disorders.

Cognitive Deficits

TBI is associated with a plethora of cognitive deficits, some of which are more common than others. They include impairment of arousal, attention, concentration, memory, language, and executive function. Loss of memory may be for both verbal and nonverbal skills. Disturbances of executive functioning include poor planning, organizing, sequencing, and set-shifting, with impaired judgment and impulse control.

Researchers have suggested that cognitive deficits can be divided into four groups according to when they occur in relation to the phases of the TBI.^{20,21} The first is the period of loss of consciousness or coma, which occurs soon after injury. The second phase is characterized by a mixture of cognitive and behavioral abnormalities, such as agitation, confusion, disorientation, and alteration in psychomotor activity. This period is associated with inability to recall events, sequence time, and learn new information. The first two phases, which last anywhere from a few days to 1 month after injury, are a form of posttraumatic delirium.¹⁴ What follows is a 6–12 month period of rapid recovery of cognitive function, followed by plateauing of recovery over 12–24 months subsequent to the injury. The fourth phase is characterized by permanent cognitive sequelae, and includes problems with speed of information-processing, attention and vigilance, short- and long-term memory deficits, verbal and nonverbal deficits, and problems with executive functions and mental inflexibility. This phase has also been described as “dementia due to head trauma.”

The cognitive deficits are caused by the cumulative effects of focal and diffuse brain damage.¹⁴ Cognitive out-

come depends on a number of factors, such as degree of diffuse axonal injury, duration of LOC and PTA, clinical evidence of brain stem dysfunction at the time of injury, and presence and size of focal hemispheric injury.

Treatment is multidisciplinary and includes pharmacotherapy, physical therapy, occupational therapy, recreation therapy, speech therapy, and vocational rehabilitation. Cognitive rehabilitation is also important, especially during the first 6 months after injury, and involves techniques to retrain the patient in specific domains by providing a series of mental stimuli, tests, and activities.²² Dopaminergics²³ or psychostimulants may improve deficits of arousal, poor attention, concentration, and memory. Numerous case reports are available on the efficacy of dopaminergics in treating cognitive symptoms.^{24–26} Cholinergic agents such as those developed to treat dementia are also showing promise in treating these deficits.^{27,28}

Mood Disorders

Mood disorders associated with TBI have been reported in the medical literature for a number of years. Adolf Meyer, in 1904, referred to these symptoms as “traumatic insanities,” and proposed that there might be an association between these symptoms and brain lesions.²⁹ Depression and mania are common after TBI.

Major depression occurs in approximately 25% of patients with TBI.^{30,31} Feelings of loss, demoralization, and discouragement seen soon after injury are often followed by symptoms of persistent dysphoria. Fatigue, irritability, suicidal thoughts, anhedonia, disinterest, and insomnia are seen in a substantial number of patients 6–24 months or even longer after TBI.^{32,33} Psychological impairments in excess of the severity of injury and poor cooperation with rehabilitation are strong indicators of a persistent depressive disorder.⁹ Clinical and research studies have also shown that poor pre-morbid level of functioning and past history of psychiatric illness are major risk factors for depression.³⁰ The mechanism of depression following head injury is probably due to disruption of biogenic amine-containing neurons as they pass through the basal ganglia or frontal-subcortical white matter.³⁴ The presence of left dorsolateral frontal and left basal ganglia lesions is associated with an increased probability of developing major depression.³⁰

The treatment of depression secondary to TBI is very similar to the treatment of major depressive disorder. It includes antidepressants, psychostimulants, and electroconvulsive therapy (ECT). The choice of medications must be influenced by their side-effect profile. Agents such as

TABLE 1. Neuropsychiatric sequelae of traumatic brain injury (TBI)

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|------------------------------------|
| 1. Cognitive deficits |
| 2. Mood disorders |
| a) Major depression |
| b) Mania |
| 3. Anxiety disorder |
| 4. Psychosis |
| 5. Apathy |
| 6. Behavior or dyscontrol disorder |
| a) Major variant |
| b) Minor variant |
| 7. Other |
| a) Sleep disturbances |
| b) Headache |

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serotonin-specific reuptake inhibitors (SSRIs) are safe and well tolerated.³⁵ Drugs with anticholinergic effects in general should be avoided. Psychostimulants^{36,37} and even the dopaminergics can be helpful in these cases, as they have an antidepressant effect. ECT is a highly effective mode of treatment for TBI patients refractory to antidepressants.³⁸ It is important to remember that in TBI patients, mood disorders are commonly accompanied by problems in the other categories—cognitive, behavioral, and somatic. Treatment should attempt to address as many areas as possible, and at the least, not worsen any specific area.

Mania after TBI is less common than depression but much more common than in the general population. It is seen in about 9% of patients.³⁹ Changes in mood, sleep, and activation may manifest as irritability, euphoria, insomnia, agitation, aggression, impulsivity, and even violent behavior.⁴⁰ Positive family history of affective disorder and subcortical atrophy prior to TBI are added risk factors.⁴¹ Mania is often seen in patients with right-hemispheric limbic structure lesions.³⁹

Treatment with anticonvulsants such as carbamazepine or valproate may be more effective than lithium, which is not specific to the neuropathology of TBI and may worsen cognitive impairment.⁹ Other than this, there is little empirical knowledge about the treatment of mania following TBI.

Anxiety Disorders

Anxiety disorders are common in patients with TBI and range in frequency from 11%–70%.^{42,43} All variants of anxiety disorders are seen, including generalized anxiety disorder, panic disorder, phobic disorders, posttraumatic stress disorder, and obsessive–compulsive disorder. TBI patients often experience generalized “free-floating” anxiety associated with persistent worry, tension, and fearfulness.⁴⁴ Increased activity of the aminergic system and decreased activity of the GABA inhibitory network is the proposed mechanism for the clinical manifestation of anxiety.⁴⁵ Right-hemispheric lesions are more often associated with anxiety disorder than left-sided lesions.⁴⁶

Anecdotal evidence suggests that antidepressants such as SSRIs, opioid antagonists such as naltrexone,⁴⁷ and buspirone⁴⁸ are promising in the treatment of anxiety disorders. Benzodiazepines⁴⁹ and antipsychotics⁵⁰ should be avoided because they cause memory impairment, disinhibition, and delayed neuronal recovery.

Behavioral therapy and psychotherapy are as impor-

tant as pharmacotherapy in the treatment of anxiety disorders.

Psychosis

Psychotic symptoms are not uncommon in TBI patients. A review of the literature by Davison and Bagley⁵¹ revealed that 0.7%–9.8% of patients with TBI develop schizophrenia-like psychosis. Most of these patients do not have a family history of schizophrenia. Other studies have shown that the incidence of head injury pre-dating psychotic symptoms in a population of patients with schizophrenia is about 15%.⁵² Psychotic symptoms following TBI often manifest as frank delusions, hallucinations, and illogical thinking. They may also be associated with symptoms of agitation, ideas of reference, grimacing, silly giggling, expression of odd ideas, regression, and impulsive aggressiveness.^{53,54} The psychotic features may be acute or chronic, transient or persistent, and may or may not be associated with mood disturbances.

Both right⁵⁵ and left hemispheres⁵⁶ have been implicated in the genesis of psychotic symptoms. It is important to remember that psychosis is a symptom, not a diagnosis or etiology.

A rational approach based on our knowledge of the neuropathology of TBI must be applied when choosing treatment options. For instance, when there is a suggestion of left-temporal involvement, there may be benefit from the use of an anticonvulsant. Delusional-type symptoms that seem more related to cognitive and behavioral impairments from frontal lobe dysfunction can benefit from dopaminergics. Neuroleptics, if administered, should be given in low doses, as animal studies have shown impaired neuronal recovery.^{50,57}

Apathy

Ten percent of patients tend to have apathy without depression, and 60% have some degree of apathy and depression following TBI.⁵⁸ Apathy refers to a syndrome of disinterest, disengagement, inertia, lack of motivation, and absence of emotional responsiveness. The negative affect and cognitive deficits seen in patients with depression are not seen in patients with apathy. Apathy may be secondary to damage of the mesial frontal lobe.⁵⁹ It often responds well to either psychostimulants, dextroamphetamine, amantadine, or bromocriptine.^{24–26,60}

Behavior Dyscontrol Disorder

Major variant. A complex syndrome, with mood, cognitive, and behavioral manifestations is seen in a number of patients after TBI.⁶¹ This occurs in both the acute and chronic stages after TBI and in patients with mild, moderate, and severe injury. Its prevalence is about 5%–70%.¹⁹ Because the major feature of the syndrome is dyscontrol of emotion, behavior, and cognition, we prefer the term *behavior dyscontrol disorder, major variant* to define the syndrome (Table 2).

Behavior dyscontrol disorder may be due to the effects of both focal and diffuse brain injury that results in a disruption of neuronal network, creating lapses in cognitive functioning and coarsening of behavior. Focal damage to the orbital–frontal area causes disinhibition, and injury to the dorsal convexity of the frontal lobe causes dysexecutive symptoms.⁵⁹ Damage to the temporal lobes causes emotional lability and memory problems.⁶⁰

A multidisciplinary approach should be maintained in treating these patients. They would benefit from a combination of environmental modification strategies;⁶² behavioral therapy, including positive and negative reinforcement; vocational training;⁶³ supportive psychotherapy; and family therapy.⁶⁴ Pharmacotherapy for behavior dyscontrol disorder would include use of dopaminergic agents, psychostimulants, opioid antagonists, SSRIs, high-dose beta-blockers, buspirone, trazodone, and anticonvulsants.^{60,65}

Minor variant. *Behavior dyscontrol disorder, minor variant*, or post-concussion syndrome (PCS), is the most commonly diagnosed entity following TBI. The syndrome is poorly defined and has been a source of controversy for a number of years. It refers to a cluster of signs and symptoms that often follows mild TBI but can occur with injury of any severity.⁶⁶ LOC is not necessary for its development.⁹ The symptoms of PCS can be broadly divided into somatic, cognitive, and mood symptoms (Table 3).⁹

Most patients recover within 3–6 months after injury.⁶⁷ However, about 15% of patients will have symptoms last-

ing longer than 1 year.^{68,69} The underlying pathogenesis is thought to be diffuse axonal injury from acceleration and deceleration forces. Interestingly, however, in some patients, the neurologic exam, neuropsychological testing, and neuroimaging studies have all been normal. Case reports of positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) studies are available that have shown focal abnormalities of glucose uptake and regional cerebral blood flow, respectively.^{70,71} As far as we know, case-controlled studies of large series of patients are not available. Functional magnetic resonance imaging (fMRI) studies might be able to shed light on this controversial syndrome. The perplexing question is whether PCS is really a separate entity with specific features or is merely a milder version of the behavior dyscontrol syndrome.

The management of this disorder should be practical and holistic. Education and support of patients and family members should be associated with supportive and behavioral psychotherapy, occupational and vocational intervention, and social skills training. If the patient is experiencing significant cognitive or emotional difficulties, he or she should be evaluated for an affective or anxiety disorder and treated appropriately.

Others

TBI patients may present with a variety of other symptoms, such as sleep disturbances or headaches. Careful evaluation of these patients should be done to ascertain if they are just isolated symptoms or if they are part of a syndrome. Treatment should be aimed at a specific disorder rather than vague symptoms.

TABLE 2. Behavior dyscontrol disorder, major variant

Mood	Cognition	Behavior
Irritability	Impaired attention	Impulsivity
Rage	Impaired memory	Aggressivity
Anger	Poor executive function	Hyperactivity
	Impaired judgment	Hyperphagia
	Distractability	Pica
	Conceptual disorganization	

TABLE 3. Behavior dyscontrol disorder, minor variant

Mood	Cognition	Somatic Symptoms
Depression	Impaired memory	Headache
Anxiety	Decreased attention	Nausea
Irritability	Decreased concentration	Dizziness
	Dysexecutive function	Vertigo
	Conceptual disorganization	Diplopia
		Insomnia
		Deafness
		Tinnitus
		Light sensitivity
		Noise sensitivity
		Fatigue
		Dyscoordination

TREATMENT OF NEUROPSYCHIATRIC SEQUELAE OF TBI

Treatment of neuropsychiatric sequelae of TBI is complicated. It includes pharmacological therapy and rehabilitative interventions, which are equally important. Rehabilitation should begin on the day of the injury and continue until the patient is stable or has reached his or her pre-injury baseline. Rehabilitation is multifaceted. It includes cognitive rehabilitation, behavioral treatment, social skills training, vocational training, individual therapy, group therapy, and family therapy. In this review, we will not be discussing the extensive array of different rehabilitative measures; we will focus our attention only on the discussion of psychopharmacology in TBI patients. The overview certainly does not encompass all the drugs used in brain-injured patients, but includes only the most commonly administered medications.

The literature review reveals that there have been very few randomized controlled studies of neuropsychiatric sequelae of TBI. Most reports in literature are either anecdotal reports or uncontrolled small-series case studies. In general, TBI patients are very sensitive to medications; hence, treatment should be initiated at low doses with gradual increase. Careful and close monitoring of patients during treatment is mandatory. The commonly used medications in brain-injured patients are psychostimulants, dopaminergic agents, and antidepressants, and other drugs, such as opioid antagonists, beta-blockers, and anticonvulsants.

Psychostimulants

Methylphenidate and dextroamphetamine are the commonly used psychostimulants. They act by increasing catecholamine activity by blocking the reuptake of norepinephrine and dopamine.⁶⁵ Side effects include paranoia, dysphoria, agitation, and irritability. Methylphenidate is usually initiated at 5 mg bid and dextroamphetamine at 2.5 mg bid. The maximum dose of both drugs is 60 mg/day.

Anecdotal reports have demonstrated the efficacy of psychostimulants in the treatment of inattention, distractibility, disorganization, hyperactivity, impulsivity, hypoarousal, apathy, and hypersomnia.^{24,37,72} One double-blind, placebo-controlled cross-over study of methylphenidate in 15 TBI patients showed improvement in mood and cognition in 14 of those patients.⁷²

Dopaminergic Agents

TBI is frequently associated with disturbances of dopamine transmission, which persists for many years after

injury.¹⁷ The frontal lobes are especially rich in dopamine, and their frequent involvement in TBI is associated with decreased dopamine activity. Amantadine, bromocriptine, and levodopa are commonly used dopaminergic agents.

Amantadine was first used in the 1960s for treatment of influenza and was later found to have antiparkinsonian actions.⁷³ It enhances release of dopamine, inhibits reuptake, and increases activity at the postsynaptic receptors.⁷⁴ Also, it is an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, and this property might protect neuronal cells against excitotoxicity.⁷⁴ Side effects of amantadine include confusion, hallucinations, edema, and hypotension. Optimal doses are found to be between 50 mg/day and 400 mg/day. Case reports have shown that amantadine is useful in the treatment of mutism, impulsivity, and aggression, and helpful for information-processing, apathy, and inattention.⁷⁴ Gualtieri⁶⁰ studied the effects of amantadine in 30 severely impaired TBI patients 2–144 months after injury. Sixty-three percent were noted to have improvement in symptoms of agitation, distractibility, emotional lability, and aggression.⁷⁴

Levodopa and bromocriptine are both dopamine agonists. They have been studied in small, uncontrolled case studies and have been found to be effective in the treatment of mood, cognition, and behavior.^{75,76} Lal et al.⁷⁵ studied the effect of L-dopa/carbidopa in 12 moderate or severe TBI patients and found functional cognitive and behavioral improvement. Common side effects of these medications include nausea, psychosis, and sedation. The dose of L-dopa/carbidopa varies from 10/100 mg to 25/100 mg qid. Bromocriptine is initiated at 2.5 mg/day and gradually increased to tolerable doses.

Antidepressants

SSRIs are useful in the treatment of depression, mood lability, and impulsivity.⁹ However, no placebo-controlled, double-blind case series is available to demonstrate the efficacy of these medications. Tricyclics and monoamine oxidase inhibitors are generally not preferred in the treatment of TBI patients because of their anticholinergic side effects and drug–food interactions, respectively. Saran⁷⁷ conducted a cross-over study of phenelzine and amitriptyline in patients with minor brain injury and found no response. Studies have shown that trazodone is useful for agitation and sleep.⁷⁸ For information about and dosage of these drugs, the reader is advised to refer to the psychopharmacology chapter in *Neuropsychiatry of Traumatic Brain Injury*.⁶⁵

Anticonvulsants

The role of anticonvulsants in the treatment of neuropsychiatric sequelae of TBI are multiple. They are used to treat seizure disorder, mood lability, mania, impulsivity, aggression, and rage.^{79,80} Carbamazepine and valproic acid are most commonly used and found to be equally beneficial. No large-scale controlled studies are available to demonstrate the efficacy of these drugs. Phenytoin and barbiturates decrease cognitive function and motor performance⁸¹ and, hence, are not recommended. For information about and dosage of these drugs, the reader is advised to refer to the psychopharmacology chapter in *Neuropsychiatry of Traumatic Brain Injury*.⁶⁵

Other Agents

Studies have shown that naltrexone, an opioid antagonist, in doses of 50 mg–100 mg/day may be useful in

treating self-injurious behavior.⁸² A study on three bulimic TBI patients⁸³ reported its efficacy.

Buspiron, a selective serotonin antagonist is useful in the treatment of anxiety disorders and aggression in doses of 45 mg–60 mg/day.⁸⁴

Similarly, beta-blockers, such as propranolol, have also been used to treat aggression and violent behavior.⁸⁵

CONCLUSION

Patients with traumatic brain injury are often referred to as “the walking wounded,” because a number of them have persistent neuropsychiatric sequelae. Even though they appear physically “normal,” they are disabled personally, socially, and occupationally. Ideally, treatment of these patient should involve a multidisciplinary approach, with the neuropsychiatrist working in close collaboration with the patient, family, neurologist/neurosurgeon, psychiatrist, social worker, and the staff of community groups such as the local chapter of the brain injury association.

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