# Depression and Cognitive Complaints Following Mild Traumatic Brain Injury

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Traumatic brain injury (TBI) is a common occurrence with multiple possible neuropsychiatric sequelae, including problems with cognition, emotion, and behavior. While many individuals experience significant improvement over the first months following mild TBI, a nontrivial minority will develop persistent, functionally impairing post-TBI symptoms. Depression and cognitive impairment are among the most common such symptoms, and they may respond to a combination of rehabilitative and pharmacologic treatments. This article discusses the clinical approach to treating an individual with depression and cognitive complaints following mild TBI. Recommendations regarding the diagnosis, evaluation, and treatment of these problems are offered.

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Traumatic brain injury (TBI) refers to a physiologically significant disruption of brain function resulting from the application of external physical force, including acceleration/deceleration forces. Evidence of disrupted brain function at the time force is applied may include loss of consciousness; loss of memory for events immediately before (retrograde amnesia) or after (anterograde amnesia) the event, collectively referred to as posttraumatic amnesia; an alteration in mental state ("dazed and confused"); a focal neurological deficit; or some combination of these (1, 2). TBI severity is divided into mild, moderate, and severe categories, primarily on the basis of the duration of loss of consciousness, duration of posttraumatic amnesia, and/or Glasgow Coma Scale (3) score at the time of admission to the emergency department or hospital. Mild TBI describes injuries that result in an admission Glasgow score in the range of 13–15; that produce a loss of consciousness of less than 30 minutes, if loss of consciousness occurs at all, and after which Glasgow scores are in the range of 13–15; and/or after which the duration of posttraumatic amnesia is less than 24 hours. Injuries that result in an admission Glasgow score <13 or that produce a duration of loss of consciousness or posttraumatic amnesia that exceeds these criteria are categorized as moderate or severe (1).

Each year in the United States, approximately 1–2 million people sustain a TBI (4, 5); most of these (about 80%) are mild TBIs (5). Among U.S. military and civilian personnel serving in Iraq and Afghanistan, TBI is among the most common injuries, with an estimated 15%–20% of soldiers experiencing a mild TBI during their deployment in these theaters (6, 7).

Post-TBI cognitive, emotional, behavioral, physical, and psychosocial problems (collectively referred to here as "neuropsychiatric") are a frequent and substantial source of at least temporary disability and stress to TBI survivors and their families (8, 9). These post-TBI neuropsychiatric impairments contribute to disability after TBI, which becomes a chronic problem for an estimated 3.17 million Americans (10). Although the majority of individuals with mild TBI will recover fully, even without specific intervention (11, 12), a nontrivial minority of persons with mild TBI develop chronic posttraumatic neuropsychiatric problems and significant disability (13).

## Pathophysiology

Injury to the brain occurs as a result of contact (or impact) forces, inertial (acceleration or deceleration) forces, or both (14). The anterior and inferior frontal and temporal areas of the brain are those most commonly and most severely affected by impact forces (15). Inertial, and particularly rotational, forces stretch and strain white matter in these and other areas (the upper brainstem, the parasagittal white matter of the cerebrum, the corpus callosum, and the gray-white matter junctions of the cerebral cortex), resulting in diffuse (or, more accurately, multifocal) axonal injury (16).

The conflicts in Iraq and Afghanistan, as well as the use of explosive devices in other regions of political unrest, have called attention to the effects of blast-related TBI (13). Although primary blast can cause brain injury, the effect of primary blast is greatest at air-tissue interfaces. Thus, primary blast most often damages air-filled organs, such as the lungs and colon, or those at air-fluid (tissue-density) interfaces, such as the tympanic membranes and the eyes (17, 18). In the absence of a blast wave of a magnitude sufficient to damage the most blast-vulnerable organs, the effect of blast on the brain is uncertain and is a

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**An independent contractor working in a war zone complains of mood, sleep, energy, and cognitive problems persisting several months after exposure to a bomb blast.**

Mr. K, a 49-year-old married man who worked as an independent contractor in Afghanistan, presents with depressed mood, sleep disturbance, fatigue, and cognitive complaints that developed after the vehicle in which he was riding sustained severe damage by a roadside bomb 6 months ago. He has fragmentary memory of this incident: he recalls driving that morning toward the area where the blast occurred, but he does not recall the explosion itself. He recalls "bits and pieces" of the period during which he was extricated from the damaged vehicle, and he recalls hearing a helicopter. His recall is better, although incomplete, for the events of that evening, when he was in the hospital for observation. He remembers having a headache, feeling very tired and cognitively "slow," and being quite irritable with the nursing staff. Although he had a laceration over his forehead, presumably from hitting the windshield of the vehicle, there was no evidence of other bodily injury that would be consistent with a primary blast injury (e.g., no pulmonary, gastrointestinal, or tympanic membrane injury and no conjunctival hemorrhages). He was discharged from the hospital the next morning and returned to the United States to recuperate and to begin a new job assignment.

Over the following week Mr. K's headache abated, and it recurred only occasionally thereafter. However, he continued to experience sleep disturbances (early and middle insomnia), fatigue, slowness of thinking, and difficulty with "concentration and memory." These problems interfered with his ability to meet the demands of his job; tasks that he had previously performed easily and quickly required substantially more time and were often completed with errors. He had difficulty keeping track of his daily tasks, frequently forgot appointments with clients and supervisors, and had difficulty concentrating during tasks and meetings. The effort to maintain even passable performance exacerbated his fatigue and sleep difficulty. These problems had not improved substantially after 1 month and were complicated by increasing irritability, dysphoria, lowered self-esteem, and pessimism. Over the following several months, his mood, sleep, energy, and cognitive problems worsened and led him to take a medical leave of absence from his job. Because of the lack of improvement in his health and functioning, and at the insistence of his wife and with the support of his employer, he presented for psychiatric consultation.

On interview, Mr. K reported feeling persistently sad and irritable, and he described himself as less able to take pleasure in "the simple things," such as spending time with his wife and children. He felt ashamed of his inability to work and of the "weakness" that he believed his "stalled" recovery reflected. In recent months, his ability to initiate and maintain sleep, his daytime fatigue, his concentration and memory, and his tendency to become "drained" by sustained cognitive effort had worsened with his declining mood. He denied symptoms consistent with posttraumatic stress disorder, such as hyperarousal, recurrent experiences of the trauma (nightmares or flashbacks), emotional numbing, or avoidance behaviors. There was no litigation involved, and his employer was fully supportive of his leave from work and his seeking treatment.

Findings were normal on the elementary neurological examination. The patient performed slowly but without errors on the Mini-Mental State Examination. A comprehensive neuropsychological battery demonstrated only slow (but errorless) performance on a test of executive function (Trail Making Test, Part B) and a few errors of omission on a vigilance task. An MRI of the brain was read as "normal for age."

Mr. K was able to enter a program of cognitive rehabilitation. Treatment with citalopram led to improvement in his mood, and residual problems with speed of processing and memory responded to methylphenidate and donepezil, respectively. Although his symptoms did improve, he was not able to resume his previous level of activity at work or at home. Rehabilitative interventions included modifying his work environment (i.e., making it quieter), developing compensatory strategies designed to help organize his tasks and to facilitate memory with written and computer-based reminders, and modifying his daily schedule to include breaks every few hours. Similar interventions were implemented at home. Additionally, his wife was provided with education about Mr. K's traumatic brain injury, his neuropsychiatric problems, and the expected course of his recovery. She was also trained to facilitate the patient's continued use of rehabilitative interventions. With this combination of treatments, Mr. K and his wife reported that his functioning, both at work and at home, and their quality of life improved.

matter of controversy (18). Secondary and tertiary blast effects are common mechanisms of blast-related TBI, affecting the brain via contact and inertial forces—for example, the sudden acceleration/deceleration and rotation of an individual in a vehicle displaced by the force of the blast or by objects driven by the blast through the vehicle and against the individual's head.

Biomechanical injury is accompanied by a cascade of injurious intra- and extracellular processes (14, 16). Injury-induced calcium and magnesium dysregulation, excitatory amino acid excesses, calcium-regulated protein activation, mitochondrial dysfunction, free-radical formation, and proteolysis are major elements of this postinjury cytotoxic cascade and contribute to traumatically induced neuronal injury and cell death. TBI also induces excessive neurotransmitter release, including functionally disruptive elevations in cerebral glutamate, acetylcholine, dopamine, norepinephrine, and serotonin levels (19). Although intracerebral levels of most of these neurotransmitters appear to normalize in the days to weeks following

**TABLE 1. Brain-Behavior Relationships Relevant to Understanding the Neuropsychiatric Sequelae of Traumatic Brain Injury**

| Structure | Function(s) | Consequence(s) of Injury |
|---|---|---|
| Rostral and ventral brainstem, thalamus | | |
| Reticulothalamic system | Arousal | Impairments of consciousness |
| Reticulocortical system | Arousal, facilitating cortical activity, attention | Hypoarousal, inattention, impaired information processing |
| Hypothalamus | Autonomic, neuroendocrine, circadian, and some lower-level social functions | Dysautonomia, thermoregulation problems, altered feeding behaviors, endocrine dysfunction, sleep-wake cycle disturbances, pathological affect (laughter or anger) |
| Ventral forebrain | Cholinergic supply to medial temporal and neocortical areas | Impaired information processing in multiple cognitive domains, particularly attention, memory, and executive function |
| Temporal lobes | | |
| Entrorhinal-hippocampal complex | Multimodal information filtering, declarative memory, some aspects of attention and working memory | Impaired sensory gating, attention, working memory, and declarative memory |
| Amygdala | Generation of contextually relevant emotional and social behavior | Affective placidity, Klüver-Bucy-like presentations; alternatively, anxiety |
| Anterior/polar cortex | Semantic memory, semantic aspects of language, sensory-limbic integration, face recognition, social and emotional processing, "theory of mind" | Disturbances in semantic memory, functional communication impairments, impaired sensory-limbic, facial, social, and emotional processing, impaired social/empathic function |
| Frontal lobes | | |
| Ventral frontal cortices | Comportment, control of primitive ("limbic") behaviors | Disinhibition, irritability, emotional dysregulation, agitation, aggression |
| Anterior cingulate cortex | Motivation | Apathy |
| Inferolateral prefrontal cortex | Working memory | Working memory impairments |
| Dorsolateral prefrontal cortex | Executive function | Impairments in complex cognition, including executive control of attention, memory, language, motor planning, as well as sequencing, set shifting, abstraction, judgment, insight |
| White matter | Connections between cortical areas, particularly in frontal and temporal areas, facilitation of information processing | Impaired cognitive, emotional, and behavioral functions supported by the affected white matter; slow, inefficient information processing |

the injury, chronic cholinergic deficits, as well as chronic primary or secondary dysfunction in dopaminergic, noradrenergic, and serotonergic systems, appear to be relatively common consequences of TBI (19, 20).

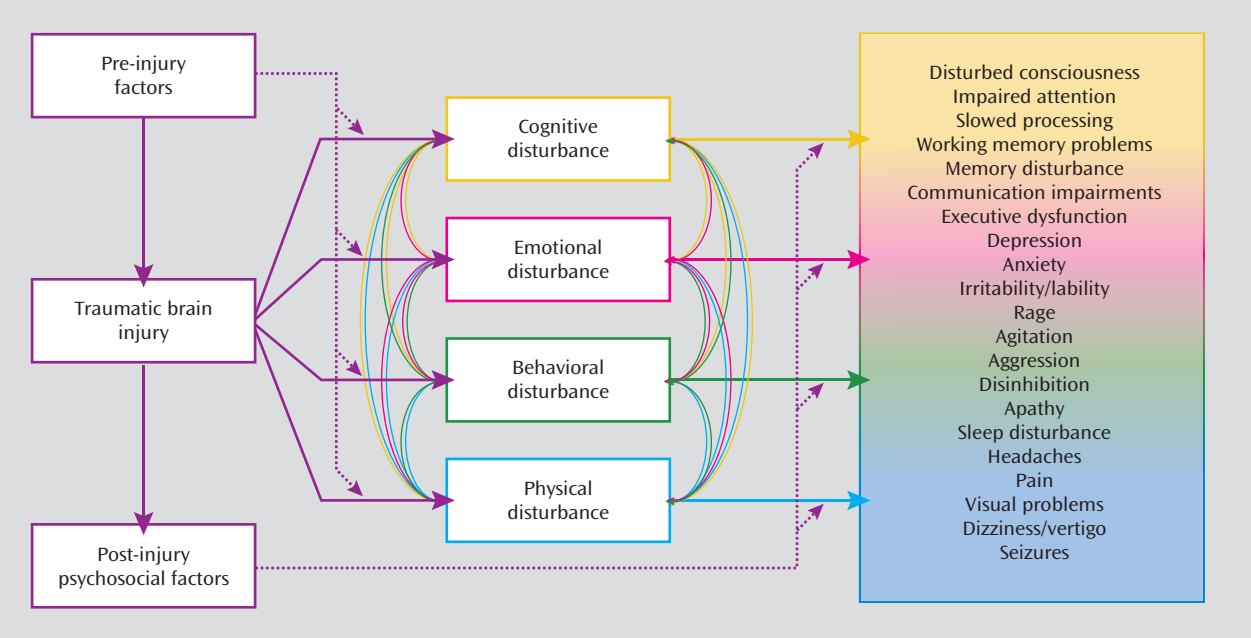
The pathophysiology of TBI is best viewed as a product not only of biomechanical forces but also of the cytotoxic cascade, neurotransmitter disturbances, and intracranial or systemic complications. Although TBI can affect any area of the brain, there is a relatively consistent pattern of regional cerebral vulnerability to injury, whether mild or more severe. That pattern of regional vulnerability explains the types of neuropsychiatric problems commonly experienced by persons with TBI (Table 1).

## Evaluation for Traumatic Brain Injury

When a patient presents for evaluation of neuropsychiatric problems that may be the result of a TBI, it is important initially to determine whether the event preceding those problems in fact produced a TBI. The patient is asked first to describe the event; the clinician then determines whether the event involved the application of external physical force (e.g., a blow to the head) or acceleration/deceleration forces (e.g., sudden start, stop, or alteration of the direction of head movement). If an external physical force was present, there needs to be evidence of immediate physiologic disruption of brain function, including loss of consciousness, posttraumatic amnesia, altered mental status of any duration (dazed, confused, "seeing stars"), and/or a focal neurological deficit (2).

There are several caveats to bear in mind when interpreting this information. First, because of the retrospective nature of evaluating a TBI—days, weeks, or months after the event—the potential for misreporting the event and its immediate neuropsychiatric manifestations is significant. Second, it is difficult to gauge accurately the mechanics, severity, and effects of an injury after the fact. In many cases, an informed but subjective clinical judgment will be required to confirm or rule out the diagnosis of TBI. Third, patients (and some clinicians) frequently misinterpret the immediate sequelae of TBI and their diagnostic implications. For example, a patient unable to recall portions of the event may misinterpret impaired recall due to posttraumatic amnesia as loss of consciousness. Fourth, the absence of evidence supporting a TBI in the medical record does not constitute evidence of absence of a TBI. Many patients with mild TBI do not go to a hospital at the time of injury. Moreover, a recent study (21) demonstrated that for those who did present to a hospital, emergency room records failed to document TBI in 56% of cases that study personnel identified as meeting the Centers for Disease Control and Prevention case definition for mild TBI. Fifth, the patient who states that he or she was "dazed," "confused," or "saw stars" may be reporting phenomena consistent with a mild TBI, an acute stress reaction, cerebral dysfunction produced by other injury-related physiologic disturbances (e.g., hypotension, hypoxia, toxin/gas inhalation), or some combination of these. Sixth, conventional clinical neuroimaging of the brain, including MRI, is often interpreted as "normal" in persons with mild TBI. A

**FIGURE 1. A Model for Understanding the Interactions Between Preinjury Factors, Injury Characteristics, and Postinjury Factors as They Contribute to Posttraumatic Neuropsychiatric Disturbances in Traumatic Brain Injury**




[a] Preinjury factors include age, gender, neurogenetics, baseline cognitive function, psychiatric conditions, substance abuse, socioeconomic environment, and risk-taking behaviors, among others. Injury characteristics, particularly location, type, and severity of neural damage, predict problems in the four domains of neuropsychiatric function: cognition, emotion, behavior, and physical function. Preinjury factors modify the development of problems in each of these neuropsychiatric domains after traumatic brain injury. The development of symptoms in one of these neuropsychiatric domains also affects the development and expression of symptoms in one or more of the other domains (e.g., depression worsens cognition, increases agitation and aggression, increases the number and perceived severity of posttraumatic physical symptoms, and so on). In combination, preinjury factors, injury characteristics, and the interactions between them produce posttraumatic neuropsychiatric symptoms (a partial list of which is presented on the right side of the figure). Postinjury factors, such as social support, timely medical and rehabilitative treatments, socioeconomic status, and medicolegal issues, also influence the expression, persistence, and remission of neuropsychiatric symptoms. Used with permission from Silver JM, Arciniegas DB: Pharmacotherapy of neuropsychiatric disturbances, in Brain Injury Medicine: Principles and Practice. Edited by Zasler ND, Katz DI, Zafonte RD. New York, Demos Medical Publishing, 2008, pp. 963–994.

normal MRI of the brain after mild TBI does not suggest the absence of injury but instead indicates only that any changes in the brain caused by the TBI are below the detection threshold of conventional clinical MRI. There are techniques that may increase the sensitivity of MRI to changes in brain structure resulting from mild TBI, including fluid-attenuated inversion recovery, gradient recalled echo, and susceptibility-weighting techniques, as well as the use of high-field (3-T) scanners. Recent work suggests that diffusion tensor imaging is a promising method for detecting alterations in the integrity of white matter resulting from mild TBI (22, 23), although its application in clinical practice will require refinement to determine its usefulness as a diagnostic measure.

The tendency of medical personnel to miss or misunderstand mild TBI and its consequences is shared by the general public (24, 25). Such misconceptions raise suspicion and doubt about the veracity of TBI survivors' clinical complaints, fueled, in part, by portrayals of mild TBI in cartoons and movies as "head injuries" or "concussions" that produce little immediate impairment and from which unrealistically rapid and complete recoveries are made.

After a diagnosis of TBI is made, the next step in the evaluation is to characterize the clinical problems with which the patient presents as well as the relationship of these problems, if any, to the TBI. The neuropsychiatric sequelae of mild TBI include problems with cognition (attention, concentration, executive functioning, memory, and speed of information processing) (19); psychiatric symptoms (personality changes, affective disorders, anxiety disorders, psychosis, sleep disorders, aggression, and irritability) (26), and physical problems, such as headache, chronic pain, vision impairment, dizziness, and, rarely, epilepsy (27). Figure 1 describes the most common posttraumatic neuropsychiatric problems following TBI. While the development and persistence of these symptoms are often described as a "postconcussion syndrome," these symptoms occur in all severities of TBI. Moreover, it is not clear that they conform to the concept of a "syndrome": the development of each symptom is not clearly linked to that of any other, and the symptoms' resolution and response to treatment are frequently uncoupled; that is, they do not necessarily follow the same recovery trajectory (28).

In general, relatively rapid recovery is expected after mild TBI (see reference 27 for a review), with about half of patients recovering fully by the end of the first month and 80%–90% recovering by 6–12 months after sustaining the injury. Nonetheless, it is our practice to institute treatment

when functionally significant neuropsychiatric symptoms are present. Education, counseling, and rehabilitative interventions may facilitate recovery and lessen the likelihood that the patient will develop persistent postconcussive symptoms (29, 30), and hence these are the initial components of neuropsychiatric treatment in this population. Given the absence of compelling evidence that medication treatment hastens recovery in mild TBI, we recommend that the decision to initiate pharmacotherapy be decided in partnership with the patient and his or her family. The goals of pharmacotherapy are to reduce the effects of such symptoms on the patient's functioning, quality of life, and recovery and to limit the likelihood that the symptoms will become a chronic problem and contribute to long-term disability. Expeditious treatment of depression after TBI is particularly important, because its successful treatment may also alleviate other postconcussive symptoms, such as anergia, insomnia, irritability, and cognitive impairments; reduce suicidal thoughts and/or behavior; and improve psychosocial function and quality of life.

## Depression Following Traumatic Brain Injury

Estimates of posttraumatic depression range from 10% to 77% (see reference 31 for a review). Although depression occurs most often in the first year after TBI, the risk of developing depression remains elevated for decades thereafter. Preinjury factors (such as mood and anxiety disorders, psychosocial dysfunction, and alcohol abuse), injury factors (such as left ventrolateral and dorsolateral injury and serotonergic dysfunction), and postinjury factors (such as postconcussive symptoms, psychosocial dysfunction, and lack of social supports) contribute to the development of depression after TBI, although the relevance of each factor varies among patients (32). Early posttraumatic depression may be more strongly related to a host-injury interaction, whereas late posttraumatic depression may be more strongly influenced by psychological and psychosocial factors (33–35).

Depression after mild TBI is associated with self-reported increases in the number and perceived severity of other postconcussive symptoms, including headache, dizziness, and blurred vision (36–38). In persons with mild or more severe TBI, depression also increases anger, aggression, the risk of suicidality, and cognitive dysfunction (37, 39–41). However, patient perceptions of impaired daily functioning and experience of other psychosocial changes after TBI may exacerbate depressive symptoms (42).

### *Treatment of Depression Following TBI*

It is appropriate to use the standard diagnostic criteria for depression when evaluating persons with TBI (43–45). Although many factors may produce or contribute to apparent depressive symptoms, such as sleep disturbance, fatigue (anergia), difficulty with concentration, and anhedonia (apathy), when there are sufficient symptoms to merit a diagnosis of depression—regardless of their possible causes—treatment should be initiated. Treatment should be promptly initiated both to improve mood and to mitigate its adverse effects on cognitive, behavioral, physical, and psychosocial functioning (36, 38, 40, 41, 46).

**Pharmacotherapy.** Pharmacotherapy may not only alleviate the mood disturbance but also reduce other postconcussive symptoms and the patient's experience of the severity of such symptoms (36). When pharmacotherapy is initiated, a "start low and go slow" approach is recommended. Common clinical experience, as well as a limited body of literature (19, 27, 31), suggests that persons with TBI may be more susceptible to the side effects of many psychotropic medications, suggesting a heightened need for vigilance for such effects when prescribing psychotropic agents in this context. Additionally, no medications have been approved by the U.S. Food and Drug Administration specifically for the treatment of post-TBI depression, or for any other posttraumatic neuropsychiatric problem. The use of these agents is therefore "off-label" and will in each case be a matter of empiric trial. Nonetheless, the literature describing the treatment of posttraumatic depression is a useful guide to treatment selection.

As reviewed by Warden et al. (47), several studies, mostly small and open-label, suggest that the selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants may improve depression following TBI. Given concerns about the tolerability of tricyclic antidepressants, particularly their potentially adverse anticholinergically mediated effects on cognition (19), the SSRIs are generally regarded as the first-line agents for treatment of depression following TBI (47).

Among the SSRIs, the available evidence favors sertraline (25–150 mg/day) (36, 48) or citalopram (>20 mg/day) (46). Ashman et al. (49), in a 10-week, double-blind, placebo-controlled study of 52 patients with remote, predominantly moderate to severe TBI, observed significant improvements in depressive symptoms in those treated with 25–200 mg of sertraline daily (mean dose not specified) or placebo. With treatment response defined as a change of 50% or more in Hamilton Depression Rating Scale score, 59% of patients receiving sertraline responded, while only 32% of those treated with placebo responded. Although the magnitude of improvement and the number of treatment responders were similar to those observed in pharmacotherapy studies performed in patients with idiopathic major depressive disorder, the response rate did not differ significantly between the number of sertraline and placebo responders. This observation most likely reflects a sample size inadequate to detect a significant difference in responder rates. The mean dose of sertraline received by these patients was not reported in the study, leaving uncertain the adequacy of antidepressant dosing.

Other SSRIs may be used to treat depression after mild TBI, although the literature provides little guidance regarding their efficacy and tolerability in this population. In everyday practice, the effectiveness and tolerability of fluoxetine does not appear to differ from that of the other SSRIs. However, its robust inhibition of cytochrome P450 (CYP450) 2D6, 2C19, and 3A, its metabolism to norfluoxe-

tine (also an inhibitor of the P450 isoenzymes), and the prolonged half-life of this active metabolite are concerning: the risk of drug-drug interactions or metabolism-related adverse events may be higher with this SSRI than with sertraline or citalopram. Paroxetine, also a potent inhibitor of CYP450, may impair cognitive function even in healthy adults, most likely as a result of its antimuscarinic effects (50). Paroxetine therefore is best used with caution, if at all, in persons with posttraumatic depression and cognitive complaints.

The efficacy and tolerability of other antidepressants (including "dual action" antidepressants and bupropion) in this population has not been established, but common clinical experience suggests that the benefits and adverse effects of most of the newer-generation antidepressants are similar to those of the SSRIs. The propensity of bupropion to reduce seizure threshold is a concern in the first-line use of this agent, although the risk of early and late seizures after mild TBI is relatively low (51), and the risk of seizures with bupropion appears to be restricted to the immediate-release formulation (52). If bupropion is used in patients with mild TBI, preference should be given to its sustained-release formulation, and vigilance for treatment-related seizures should be maintained.

In addition to effects on depressive symptoms, SSRIs may improve comorbid posttraumatic somatic, behavioral, and cognitive problems. Fann et al. (36) demonstrated sertraline-related improvements in postconcussive symptoms, including headache, fatigue, and sleep disturbance, as well as reduction in the perceived severity of injury and improvement in psychosocial functioning. Fann et al. (41) also reported that sertraline-related improvement in post-TBI depression was accompanied by improvements in psychomotor speed, recent verbal memory, recent visual memory, and general cognitive efficiency, as well as patients' perception of the severity of their cognitive problems. Horsfield et al. (53) observed similar benefits in a small series of patients with TBI treated with fluoxetine.

The benefits of antidepressants for posttraumatic cognitive impairments have not been observed in all studies. Lee et al. (54), comparing the effects of sertraline and methylphenidate on depression after mild to moderate TBI, reported reductions of depressive symptoms with both agents, but more substantial improvements in cognition and daytime fatigue with methylphenidate. Similar benefits of methylphenidate monotherapy for depression after TBI have been reported by other authors (55). These observations suggest that some patients with significant depression, fatigue, and cognitive impairments after TBI may experience improvements in all of these domains in response to a single agent, methylphenidate. In practice, however, the use of methylphenidate in the treatment of depression is generally limited to augmentation of a standard antidepressant and targets residual depressive, anergic, or cognitive impairments.

**Psychotherapy.** Psychological and social factors contribute to the development and persistence of posttraumatic depression. Education regarding TBI and recovery expectations, reassurance, and frequent support are associated with better outcomes during the first year after the injury was sustained (29, 30), and multidisciplinary treatment may be particularly useful for individuals with mild TBI and prior psychiatric problems (56). Cognitive-behavioral therapy (CBT) may be useful for a variety of posttraumatic neuropsychiatric problems. CBT has been observed to decrease depression, anxiety, and anger and to improve problem-solving skills, self-esteem, and psychosocial functioning after TBI, although the benefits of such psychological improvements on depression are observed inconsistently (57–59).

Spouses, families, and caregivers of persons with TBI frequently require psychotherapeutic intervention to aid them in maintaining both their own psychological health and that of their injured family member. Depression occurs more frequently in caregivers of persons with TBI (60), and posttraumatic depression is strongly associated with significant family dysfunction (61). Use of problem-solving and behavioral coping strategies by the patients' families can decrease the severity of depression (62). Thus, engaging spouses, family members, and other care providers in the treatment of posttraumatic depression is essential. Peer support programs for persons with TBI and their families increase their knowledge about TBI, improve general outlook, enhance their ability to cope with depression, and improve quality of life after TBI (63).

## Treatment of Cognitive Impairment

After treating depression, treatment of residual cognitive problems is appropriate. Cognitive rehabilitation, usually provided by an occupational therapist, speech therapist, or neuropsychologist, is most useful for the development of compensatory strategies to address difficulties with memory, attention, interpersonal communication skills, and executive function (64, 65). Cognitive rehabilitation appears best suited to patients who have mild to moderate cognitive impairments, who have relatively well preserved functional independence, and who are motivated to engage in and rehearse these strategies. Pharmacotherapy may be a useful adjunct to cognitive rehabilitation.

The neuroanatomy and neurochemistry of TBI yield two general approaches to the pharmacotherapy of posttraumatic cognitive impairments: catecholaminergic augmentation and cholinergic augmentation (19). Methylphenidate augments cerebral catecholaminergic function and is the first-line treatment for impaired speed of processing; it may also improve arousal and, to a lesser extent, attention and memory (47). Pharmacologically similar agents, such as dextroamphetamine, may afford comparable benefits, although there are few studies offering evidence to support their use in this population.

Methylphenidate generally takes effect quickly (within 0.5–1 hour) and loses effect after a few hours. Therefore, the first issue in the administration of this agent is to determine its optimal dose and dosing frequency. Treatment

**Summary and Recommendations**

Traumatic brain injury is associated with an increase in the relative risk of developing a variety of psychiatric disorders, particularly depression and cognitive impairment. This relationship is best understood in the context of both the neuropathophysiology and the typical profile of regional brain injury associated with biomechanical trauma, as well as the psychosocial sequelae that often follow the injury and their attendant effects on social, vocational, and family functioning. Thus, in many ways TBI is a prototypical neuropsychiatric disorder.

There remains much that is incompletely understood about neuropsychiatric and functional outcome after TBI. Individuals may have disparate long-term outcomes after seemingly similar injuries. Probable contributors to this variance include preinjury host factors, injury-specific biomechanics (72), and genetic factors (73). Further investigation of these matters is needed to improve our ability to understand, identify, and more effectively treat those individuals at risk for poor outcomes following mild TBI.

Currently, a multidimensional approach is critical to the assessment and treatment of the neuropsychiatric sequelae of mild TBI. The most important initial step is accurate diagnosis, which can be challenging in cases of mild TBI. A combination of psychotherapeutic and pharmacologic interventions can alleviate many symptoms, and improved quality of life for persons with TBI and their families can be achieved through application of the approach described in this article. Psychiatrists, armed with a neuropsychiatric approach to mild TBI, are critical members of the health care team attending to persons with mild TBI and have an important role in the management of this significant public health problem.

generally begins at 5 mg methylphenidate once daily and is gradually increased, in 5-mg increments, until adequate benefits are achieved or medication intolerance occurs. Methylphenidate may induce mild increases in heart rate and blood pressure, although such changes are relatively infrequent and rarely require treatment discontinuation. Nonetheless, baseline pulse and blood pressure should be obtained and monitored until a final dosage is achieved. In patients with a history of stimulant abuse, the risks of abuse of methylphenidate should be considered carefully before undertaking treatment with this agent. While doses are often in the range of 10–20 mg twice daily (i.e., 0.15–0.30 mg/kg twice daily), some patients may require higher doses (e.g., 40 mg) and greater frequency (3–4 times a day). Individuals requiring relatively high and frequent doses of methylphenidate may benefit from use of longer-acting preparations. In such cases, it also may be useful to obtain blood levels of methylphenidate 90 minutes after ingestion to evaluate patient-specific pharmacokinetics and to use that information to guide considerations regarding the prescription of higher doses.

Placebo-controlled studies suggest that donepezil (66, 67) and rivastigmine (68, 69) may be useful in the treatment of posttraumatic cognitive impairments, and particularly memory impairments. Cholinesterase inhibitor-related improvements in attention and executive functioning have also been reported (see reference 19 for a review), and these agents are sometimes used for this purpose in clinical practice. Consistent with this suggestion, the Neurobehavioral Guidelines Working Group (47) recommended donepezil (5–10 mg daily) to enhance aspects of attention and memory for patients with moderate to severe TBI in subacute and chronic periods of recovery. Based on findings published after the Neurobehavioral Guidelines Working Group report was issued, rivastigmine (3–6 mg daily) is also suggested as an option in the treatment of chronic posttraumatic memory and perhaps attention impairments (68). In our experience and that of others (70), these agents—alone or in combination with those that augment catecholaminergic function—are also useful in the treatment of posttraumatic cognitive impairments in persons with mild TBI.

## Treating Other Comorbid Neuropsychiatric Symptoms

Many symptoms that affect individuals with TBI may persist despite the treatments described above. As illustrated in Figure 1, the development and persistence of these symptoms may reflect preinjury problems, the effects of injury, postinjury psychological or social problems, or some combination of these factors. The treatment of these and other posttraumatic neuropsychiatric symptoms is beyond the scope of this article, but information may be found elsewhere (see reference 71 for a review).

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