Addressing neuropsychiatric disturbances during rehabilitation after traumatic brain injury: current and future methods

David B. Arciniegas, MD

Traumatic brain injury (TBI) produces clinical problems and care needs that are intrinsically and unavoidably neuropsychiatric during both the early and late post-injury periods. In the acute injury period, cognitive impairments are nearly universal,[1-5] and are frequently accompanied by disturbances of emotion, behavior, and/or sensorimotor function.[1-10] Neurotrauma-induced neuropsychiatric disturbances are especially prominent among individuals who are hospitalized after TBI[7-11] and, in this subpopulation, often become chronic conditions.[12-17] The neuropsychiatric consequences of TBI

Cognitive, emotional, behavioral, and sensorimotor disturbances are the principal clinical manifestations of traumatic brain injury (TBI) throughout the early postinjury period. These post-traumatic neuropsychiatric disturbances present substantial challenges to patients, their families, and clinicians providing their rehabilitative care, the optimal approaches to which remain incompletely developed. In this article, a neuropsychiatrically informed, neurobiologically anchored approach to understanding and meeting challenges is described. The foundation for that approach is laid, with a review of clinical case definitions of TBI and clarification of their intended referents. The differential diagnosis of event-related neuropsychiatric disturbances is considered next, after which the clinical and neurobiological heterogeneity within the diagnostic category of TBI are discussed. The clinical manifestations of biomechanical force-induced brain dysfunction are described as a state of post-traumatic encephalopathy (PTE) comprising several phenomenologically distinct stages. PTE is then used as a framework for understanding and clinically evaluating the neuropsychiatric sequelae of TBI encountered commonly during the early post-injury rehabilitation period, and for considering the types and timings of neurorehabilitative interventions. Finally, directions for future research that may address productively the challenges to TBI rehabilitation presented by neuropsychiatric disturbances are considered.

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Author affiliations: Michael K. Cooper Professor of Neurocognitive Disease; Director, Neurobehavioral Disorders Program; Associate Professor of Psychiatry & Neurology, University of Colorado School of Medicine, Aurora, Colorado, USA

Address for correspondence: David B. Arciniegas, MD, Neurobehavioral Disorders Program, University of Colorado Denver, 13001 East 17th Place, Campus Box F546, Aurora, Colorado 80045, USA
(e-mail: David.Arciniegas@UCDenver.edu)

contribute substantially to post-injury disability,[16-18] and diminish the quality of life experienced by persons with TBI and their families.[17,19-21]

We suggested elsewhere[6,22] that adverse short- and long-term TBI outcomes might be mitigated most effectively by initiating neuropsychiatric evaluation and management of persons with TBI during the early post-injury (ie, the neurocritical care and inpatient rehabilitation) periods. Although the hypotheses borne of this suggestion remain incompletely tested, a complementary literature supports the potential benefits of early neuropsychiatric intervention provided to patients engaged in acute neurorehabilitation after TBI.[8,23-25] Accordingly, developing further the neuropsychiatric expertise of physicians and other specialists providing care to persons with TBI in such settings is an important objective.

Toward that end, this article addresses the evaluation and management of neuropsychiatric disturbances among persons receiving rehabilitation after TBI. Clinical case definitions of TBI are described first. The differential diagnoses of event-related disturbances of neuropsychiatric function are considered, after which the clinical and neurobiological heterogeneity of TBI are discussed. A neurobiologically anchored, neuropsychiatrically informed framework for understanding and clinically evaluating the neuropsychiatric sequelae of TBI during the post-injury rehabilitation period is offered. Consideration then is given to the types and timings of neuropharmacologic and rehabilitative treatments that follow from that framework. Finally, directions for future research that may address productively the challenges to TBI rehabilitation presented by neuropsychiatric disturbances are considered.

Clinical case definition of TBI

TBI denotes a disruption of brain function and/or structure resulting from the application of an external physical force (including biomechanical force, acceleration/deceleration forces, and/or blast-related forces).[1-5] Establishing with a reasonable certainty that a TBI occurred is a prerequisite to framing neuropsychiatric disturbances as "post-traumatic." This necessitates being familiar with and applying well-accepted clinical case definitions of TBI.[1-5,26] Among these, the American Congress of Rehabilitation Medicine (ACRM) clinical case definition[2] is the most widely used in clinical and research settings; it also serves as the foundation for more recently developed clinical case definitions.[1,3,4,26] An important shared feature of all of these clinical case definitions is that no single symptom or sign is regarded as pathognomonic of TBI. Instead, any one (or more) of several clinical features suffices as evidence of brain dysfunction that, in the context of biomechanical force application, allows assignment of a TBI diagnosis. Several of the most commonly used clinical case definitions of TBI are presented in *Table I*, along with comments on their nonshared features.

Among those nonshared features, it is important to note that the use of skull fracture as a proxy marker for in the TBI Centers for Disease Control and Prevention[5] clinical case definition reflects its intended application: public health-oriented surveillance for central nervous system injury in which diagnosis is based solely on the medical records of persons hospitalized immediately following TBI. The association between skull fracture and TBI is well described but this association is not invariant.[27] Accordingly, predicating a clinical TBI diagnosis solely on skull facture—ie, head injury in the absence of other evidence of brain injury—presents an unacceptably high risk of misdiagnosis.

All TBI clinical case definitions also exclude brain injuries resulting from birth trauma, hypoxic-ischemic (anoxic), inflammatory, toxic, or metabolic encephalopathies, primary ischemic or hemorrhagic strokes, seizure disorders, intracranial surgery, and cerebral neoplasms. While such injuries may be traumatic in a colloquial sense and/or psychologically traumatizing, they do not constitute TBI.

The differential diagnosis of TBI

The differential diagnosis of event-related neuropsychiatric disturbances is broad *(Table II)*, and their consideration is necessary before attributing these phenomena unequivocally to TBI. As noted in Kay et al[2] and Menon et al,[1] conditions other than TBI may contribute to or, in some cases, be responsible for, alterations in mental state, emotional and behavioral changes, and sensorimotor function at the time of injury. However, the presence of such conditions, including those with clinical features that mimic the acute (ie, event-related) or late neuropsychiatric manifestations of TBI, does not preclude a TBI diagnosis. In some cases, the occurrence of other conditions may explain how a TBI occurred—for example, syncope resulting in fall-related TBI, or alco-

hol intoxication while driving resulting in a road-traffic accident-related TBI. Additionally, pre-injury developmental, medical, neurological, psychiatric, and substance use problems are common among persons with TBI[28] and may interact with TBI and/or each other to alter early and late post-injury neuropsychiatric presentations.[29,30] Rendering a TBI diagnosis is therefore a matter of clinical judgment[31,32] that requires interpretation of

American Congress of Rehabilitation Medicine (1993)	Centers for Disease Control and Prevention (2002)	Department of Veterans Affairs and Department of Defense (2009)	International and Interagency Initiative toward CDE for Research on TBI and PH (2010)
Traumatically induced* physiologic disruption of brain function, as manifested by at least one of the following:	An occurrence of injury to the head that is documented in a medical record, with one or more of the following conditions attributed to head injury:	Traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force‡ that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event:	An alteration in brain function, or other evidence of brain pathology,Δ caused by an external force.‡ Alteration in brain function is defied as one of the following clinical signs:
Any period of loss of consciousness	Observed or self-reported (partial or complete) decreased level of consciousness	Any period of loss or a decreased level of consciousness	Any period of loss of or decreased level of consciousness
Any loss of memory for events immediately before or after the accident	Amnesia (ie, loss of memory for events immediately preceding the injury, for the injury event itself, and for events subsequent to the injury)	Any loss of memory for events immediately before or after the injury (post-traumatic amnesia)	Any loss of memory for events immediately before (retrograde amnesia) or after the injury (post-traumatic amnesia)
Any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused)	Objective neuropsychological abnormality¥	Any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc)	Any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc)
Focal neurologic deficit(s) that may or may not be transient	Objective neurological abnormality	Neurologic deficits (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc) that may or may not be transient	Neurologic deficits (weakness, loss of balance, change in vision, dyspraxia, paresis/plegia [paralysis], sensory loss, aphasia, etc)
	Diagnosed intracranial lesion†	Intracranial lesion	
	Skull fracture		

Table I. Commonly used clinical case definitions of traumatic brain injury. Notes: *Traumatically induced refers to injuries that result from the head being struck, the head striking an object, and/or the brain undergoing an acceleration/deceleration movement without direct external trauma to the head; †Intracranial lesion, usually identified with computed tomography or magnetic resonance imaging of the brain, includes: diffuse axonal injury; traumatic intracranial hematomas or hemorrhage (epidural, subdural, subarachnoid, or intracerebral); cerebral contusions or lacerations; or penetrating cerebral injuries (eg, gunshot wounds). ‡External force includes any of the following events: the head being struck by an object; the head striking an object; the brain undergoing an acceleration/deceleration movement without direct external trauma to the head; a foreign body penetrating the brain; forces generated from events such as a blast or explosion; or other forces yet to be defined. ¥Objective neuropsychological abnormalities are determined from mental status and neuropsychological examinations, and include disorders of mental status (eg, disorientation, agitation, or confusion) and other changes in cognition, behavior, or personality; importantly, this clinical case definition was developed for use by injury surveillance systems that anchor case ascertainment to the medical record of the hospital stay at the time of injury—and, therefore, refers to neuropsychological abnormalities that are documented in that medical record (ie, not those identified at a later date and/or in another setting). ΔOther evidence of brain pathology may include visual, neuroradiologic, or laboratory confirmation of damage to the brain; such evidence may enable a diagnosis of TBI when clinical consequences are delayed or subtle; clinical diagnosis is confounded by a difficult context (eg, battlefield TBI); or there is a need to differential TBI-induced clinical signs from those with other causes (eg, chemical warfare). CDE, common data elements; TBI, traumatic brain injury; PH, psychological health

an individual clinical history not only with respect to well-accepted TBI clinical case definitions but also in context of a comprehensive differential diagnosis of event-related neuropsychiatric disturbances.

Differential diagnosis within the category of TBI

Clinical case definitions usefully limit the range of problems that fall under the heading of TBI. Nonetheless, there remains significant phenomenological and pathophysiological heterogeneity within this diagnostic category. TBI denotes a broad range of injury types and severities as well as a host of potentially injurious biological processes,[33-37] the rates and extents of recovery from which vary with initial TBI severity and the interaction between TBI and other pre- and post-injury factors.[13,29,38-41] These other factors—ie, the brain that is injured and the events that follow TBI—are increasingly recognized as important sources of variance in TBI outcome, and their influence on post-traumatic neuropsychiatric status is considered later in this article. Incorporating those considerations into clinical practice and research requires first, however, an understanding of initial TBI severity.

The range and assessment of initial TBI severities

Characterizing TBI severity informs usefully on clinical phenomenology and narrows the range of neuropathophysiologies that are explanatorily relevant and potential targets of clinical intervention[22,29,34] (discussed further below). Initial TBI severity also informs on the prognosis for post-injury mortality, morbidity, and disability.[38,42-46] Accordingly, initial TBI severity is an important element of the body of clinical information needed when discussing prognosis and probable post-hospitalization treatment/resource needs with patients, their families, and other healthcare providers.

Although TBI severity occurs along a continuum, it is commonly described in categorical terms. For example, clinical case definitions[2,47] generally categorize TBI as mild or moderate-to-severe (ie, more-than-mild). Similarly, clinical metrics like the Glasgow Coma Scale

Event-related alterations of consciousness	Pre-injury neurobehavioral disorders (eg, dementia, delirium)
	Traumatic brain injury
	Severe dehydration and/or other causes of hypovolemia
	Hyper- or hypothermia
	Cardiovascular compromise (eg, cardiac arrest)
	Cerebrovascular events (eg, transient ischemic attack, stroke)
	Cerebral hypoxia or hypoxia-ischemia
	Generalized or complex partial seizure due to pre-established epilepsy, as well as subsequent post-ictal confusional states
	Neurotrauma-induced seizures (partial or generalized) and subsequent postictal confusional states
	Toxin inhalation
	Intoxication or withdrawal from alcohol or other substances
	Medications, including those prescribed by emergency responders, medical personnel, and/or self-administered by patients (eg, opiate analgesics, anxiolytics, sedative-hypnotics, anticonvulsants)
	Acute stress responses (eg, severe anxiety reactions, acute stress-induced dissociative states)
Event-related sensorimotor symptoms	Pre-injury sensorimotor disorders (eg, headaches, tinnitus, vertigo)
	Traumatic brain injury
	Cerebellar or brain stem injury without cerebral involvement
	Cerebrovascular events (eg, transient ischemic attack, stroke)
	Simple partial (focal motor or sensory) seizure
	Injury to sensory organs (eg, eye, inner ear, nasal tissues)
	Injury to cranial nerves
	Injury to structures of the head, neck, and/or cervical adnexa
	Spinal cord, brachial or sacral plexus, or peripheral nerve injuries

Table II. The differential diagnosis of event-related neuropsychiatric disturbances.

(GCS)[48] and/or duration of post-traumatic amnesia (the peri-injury period during which there is a dense impairment in the ability to learn new information, including events following injury [anterograde amnesia] as well as those immediately preceding it [retrograde amnesia][49,50]) often are used to assign TBI to a severity category, ie, mild, moderate, or severe[51] or subdivisions thereof *(Table III)*.[50,52-55]

Post-traumatic amnesia durations ≤24 hours are consistent with a diagnosis of mild TBI (uncomplicated or complicated) whereas durations >24 hours suggest moderate-to-severe TBI[2,4]—provided that other factors contributing to or confounding assessment of post-traumatic amnesia (eg, medications, other medical illnesses, substance withdrawal) do not better account for amnesia during this period. Recent evidence,[53] however, suggests that 1-year post-injury outcomes (defined as percent returning to productive employment) among persons with more-than-mild injuries are defined more usefully by post-traumatic amnesia durations of 1 to 14 days (70%), 14 to 28 days (40%), and >28 days (20%). These findings support regarding initial TBI severity as a continuous variable and suggest further that describing it as such may inform more usefully on injury outcomes than does strict adherence to TBI severity categories.

In short, initial TBI severity is a substantial source of within-diagnosis heterogeneity. Additionally, there is heterogeneity within the severity categories defined by GCS scores and/or post-traumatic amnesia duration, especially at the mild and severe ends of the TBI spectrum. Acknowledging this heterogeneity is needed to better understand the variability in neuropsychiatric presentations and outcomes after TBI, and may inform on the types and timings of interventions designed to improve those outcomes. This latter issue will be considered further after a brief review of the neuropathophysiological heterogeneity of TBI.

Neuropathophysiology of TBI

When an external physical force, including acceleration/deceleration forces, is applied to the head, the brain is subjected to two types of forces within the intracranial vault: inertial and contact.[37,56] Inertial forces refer to rotation, translation, angular acceleration of brain tissue within the intracranial vault. The effects of these forces are greatest: (i) at planes of brain diffuses of different density (ie, gray-white matter junctions); (ii) in areas within the skull where there is more room for free movement (ie, anterior and middle cranial fossae) and, by extension, across white matter tracts connecting brain within those areas to less mobile brain structures (ie, connections between frontal and temporal areas, between anterior and posterior areas); and (iii) where differential movement (ie, interhemispheric fissue—greatest at the anterior and posterior corpus callosum) or rotation occurs (ie, between the supra- and infra-tentorial compartments—upper brain stem and brain stem-diencephalic junction). Stretching and straining of neural tissues at these locations disrupts their function and/or structure and, in turn, incites a complex cascade of potentially injurious cellular and metabolic processes.

This cascade includes: dysregulation of calcium, magnesium, and potassium across disrupted cell membranes; biomechanically induced axon potentials; neurotransmitter and excitatory amino acid release (discussed

	Modified VA/DoD TBI Severity Classification System				
	LOC (hours)	PTA (days)	AOC (days)	GCS score (best in first 24 hours)	CT or MRI
Mild TBI	≤ 0.5	≤ 1	≤ 1	13-15	Normal
Complicated mild TBI	≤ 0.5	≤ 1	≤ 1	13-15	Abnormal
Moderate TBI	> 0.5 to < 24	> 1 to < 7	> 1	9-12	Normal or abnormal
Severe TBI	≥ 24	≥ 7	> 1	3-8	Normal or abnormal

Table III. Classification of traumatic brain injury (TBI) severity used in the Department of Veterans Affairs and Department of Defense Clinical Practice Guideline: Management of Concussion/mild Traumatic Brain injury (April, 2009), modified to include complicated mild TBI. Use of this table to designate TBI severity requires consideration of as many variables as are available, and consideration of the differential diagnosis for event-related disturbances of consciousness and/or neuroimaging findings. LOC, loss of consciousness; PTA, post-traumatic amnesia (densely impaired new learning); AOC, alteration of consciousness (eg, confusion, disorientation, slowed thinking); GCS, Glasgow Coma Scale; CT, computed tomography of the brain; MRI, magnetic resonance imaging of the brain.

below); calcium-regulated protein activation, mitochondrial dysfunction; altered cellular energetics and metabolism, free radical formation and oxidative stress; activation of proteolytic enzymes; and, in some cases, activation of cellular processes that initiate apoptosis (programmed cell death). These processes are initiated at the time of injury and gradually wane over the hours, days, or weeks thereafter.[22,34,35,57,58]

Because neurotransmitter systems are a common target of pharmacotherapies for cognitive, emotional, behavioral, and sensorimotor disturbances after TBI, additional specific comment on this element of the cytotoxic cascade is warranted. Experimental injury studies[59] and cerebrospinal fluid sampling studies among persons with severe TBI[36] identify significant neurotransmitter excesses in the early post-injury period; these include marked elevations of glutamate, L-aspartate, acetylcholine, dopamine, norepinephrine, serotonin, and γ-aminobutyric acid (GABA). This "neurotransmitter storm" appears to abate over the course of the first several weeks following severe TBI, during which levels of excitatory amino acids (eg, glutamate, aspartate) and the monoamine neurotransmitters (ie, dopamine, norepinephrine, serotonin) normalize among survivors of such injuries. The interval over which acute cholinergic excesses wane after TBI in humans is not well established, but there is at present no evidence to suggest that the time course of this process differs from that of other neurotransmitter excesses. However, early post-injury cholinergic excesses are followed by late cortical cholinergic deficits in a substantial subpopulation of patients.[60] There also is evidence of altered catecholaminergic function after TBI,[61-63] and interactions between injury-related alterations in these systems and genetically-mediated individual vulnerabilities may influence their clinical expression.

Application of an external physical force also may subject the brain to contact forces—that is, injury produced when the brain strikes the inner table of the skull, especially the bony ridges and protuberances within and between the anterior and middle cranial fossae.[37] In addition to compressive damage to brain tissue caused by forceful brain-skull contacts, local (ie, focal) vascular/hemorrhagic, cytotoxic, and inflammatory injury also is induced.

The combination of inertial forces, contact forces, and cellular/metabolic events associated with the application of biomechanical force tends to disrupt the function (and, as initial injury severity increases, the structure) of a relatively predictable set of brain areas—including, and especially, anterior and ventral frontal and temporal areas, cerebral hemispheric white matter, and the upper brain stem/brain stem-diencephalic junction. In light of the neuropsychiatric functions served by these brain structures, TBI therefore also produces a relatively predictable set of neuropsychiatric disturbances *(Table IV)*.

Although these disturbances in brain-behavior relationships are typical of TBI, the neurobiological consequences of such injuries vary greatly between patients and even within patients with clinically similar initial TBI severities.[29,64] Some, but not all, individuals with TBI experience overt structural injury; when structural injury occurs, the locations and severities of those injuries are highly variable, as are the magnitudes and durations of concomitant local and diffuse cytotoxic disturbances.[34,35,59,65] Neurophysiologically, there are at least five hypothetical sets of processes that contribute to acute alterations of consciousness and/or sensorimotor function; these are described by Shaw[59] as the vascular, reticular, centripetal, pontine cholinergic system, and convulsive hypotheses of concussion. Some of these processes may develop in the absence of disruptions of brain structure, and some elements of these also are quite transient. However, some of these evolve over time after injury and may entail chronic alterations of the function of modulatory cerebral neurotransmitter systems.[60-62] All TBIs involve some, but not all, of these processes.

Unfortunately, presently available clinical neurodiagnostics do not afford comprehensive identification of the entire spectrum of functional and structural consequences of biomechanically induced neurotrauma at the single-patient level—especially at the mild end of the TBI severity continuum and, at all levels of TBI severity, the microcellular aspects of neuropathophysiology. As such, the clinical evaluation of persons with TBI and post-traumatic neuropsychiatric disturbances necessarily leaves unaccountable a portion—perhaps, in some cases, a majority—of the variance in neuropathobiology contributing to clinical presentation.

Finally, the neuropathophysiology of TBI may be complicated by secondary neurological and systemic medical problems. Some develop as a consequence of TBI (eg, post-traumatic seizures, cerebral edema, subfalcine or transtentorial herniation, vasconstrictive ischemic infarc-

Brain areas vulnerable to TBI	Relevant structures/systems	Neuropsychiatric function(s) supported	Effects neurotrauma-induced injury or dysfunction
Upper brain stem and brain stem-diencephalic junction	Reticulothalamic system, including: pedunculopontine and laterodosal tegmental nuclei (Ch5 and Ch6); their efferent projections and their thalamic, subcortical, and cortical targets; thalamic and reticular thalamic nuclei as well as their glutamatergic and GABA-ergic projections	Arousal (wakefulness)	Impaired or absent arousal, including coma
	Reticulocortical system, including ventral tegmental area (DA), locus ceruleus (NE), median and dorsal raphe nuclei (5HT), ventral forebrain cholinergic nuclei [Ch1-4] (ACh)	Arousal, cortical orientation to novel sensory events, elementary selective attention	Diminished arousal, reduced clarity of awareness of the environment, ineffective neural engagement in information processing
Ventral forebrain	Septal nucleus [Ch1], diagonal band of Broca (vertical limb [Ch2] and horizontal limb [Ch3]), nucleus basalis of Meynert [Ch4], and their efferent pathways to cortical and subcortical targets	Attention, memory, executive function [Ch1, Ch2, Ch4] Olfaction [Ch3]	Impaired sensory gating, attention, declarative memory, and executive function Hyposmia or anosmia
Hypothalamus	Anterior, tuberal, and posterior (including mammillary) nuclei	Autonomic, neuroendocrine, circadian, memory, social, and appetitive functions	Autonomic dysfunction, impaired thermoregulation, altered feeding behaviors, endocrine abnormalities (including specific endocrine disturbances or panhypopituitarism), altered sleep-wake and other circadian cycles, pathological laughter or anger
Cerebral white matter	Upper brain stem (ie, pontine, midbrain, and mesencephalic white matter), parasagittal white matter, corpus callosum, and superficial (cortical) gray-white matter junctions	Connects cerebral, cerebellar, and brain stem structures involved in all manner of information processing; myelination facilitates speed of information transfer	Slowed and inefficient information processing; lesions to discrete pathways or tracts impairs information processing in the networks to which they contribute
	Uncinate fasciculus (white matter linking anterior temporal lobe with inferior frontal gyrus and ventral fontal lobes)	Dominant hemisphere: auditory-verbal memory proficiency Nondominant hemisphere: autonoetic consciousness (experiencing self as continuous over time)	Impaired verbal memory Impaired self-awareness, particularly as regards experience of continuous self over time

Table IV. Brain areas most vulnerable to traumatic brain injury, the neuropsychiatric functions in which they are involved, and the neuropsychiatric consequences of injury to these areas. GABA, γ-aminobutyric acid; DA, dopamine; NE, norepinephrine; 5HT, serotonin; ACh, acetylcholine; Ch, cholinergic

tions), some arise as concurrent consequences of biomechanical craniocerebral trauma (eg, epidural or subdural hematoma, subarachnoid hemorrhage, intracranial infection), and others are the result of concurrent physical injuries or medical interventions (eg, hypovolemia, hypotension, hypoxia-ischemia, systemic infection/sepsis, iatrogenic sedation). Although these are most commonly problems among persons hospitalized as a result of TBI, their development is not limited to hospitalized patients and they require consideration in all cases as potential contributors to neuropsychiatric disturbances and targets of medical and neurorehabilitative interventions.

Post-traumatic encephalopathy: a framework for addressing neuropsychiatric disturbances during TBI rehabilitation

Evaluation and treatment approaches follow logically from the philosophy within which clinical phenomena are observed and interpreted and diagnoses formulated.[66] This is particularly so when facing the diagnostic and therapeutic challenges presented by post-traumatic cognitive, emotional, behavioral, and sensorimotor (ie, neuropsychiatric) disturbances: an understanding of such problems borne of traditional guild-like perspectives of neurosurgery, neurology, psychiatry, or rehabilitation

Temporal lobes	Temporopolar cortex	Sensory-limbic integration, with associative linking of information from dorsolateral (auditory), inferior (visual), and prepiriform medial (olfactory) temporal cortices to amygdalar and insular cortices; relevant to social and emotional processing as well as semantic aspects of language	Disturbances in sensory-limbic integration, including human analogues of Klüver-Bucy syndrome; impairments in socioemotional processing, including loss of empathy; semantic aphasia; visual (object) agnosia; face processing deficits or, rarely, amnesic associative prosopagnosia
	Entorhinal-hippocampal complex	Sensory gating, declarative memory; contributions to other attentional and working memory processes	Sensory gating deficits, impaired declarative new learning; contributions to attention and working memory impairments
	Amygdala	Generation of emotion, especially fear conditioning	Disturbances in emotional learning, affective placidity, human analogues of Klüver-Bucy syndrome
Frontal lobes	Dorsolateral prefrontal cortices	Executive function, including executive control of basic aspects of cognition	Executive dysfunction, including impaired intrinsic executive function (eg, conceptualization, judgment, insight) and impaired executive control of attention (ie, alternating, divided), working memory, declarative memory (ie, impaired retrieval), language, motor planning
	Ventral (orbitofrontal) cortices	Monitoring, learning, and memory for reward values of behavioral reinforces (medial); evaluation of punishers (lateral)	Disturbances of comportment and social judgment; with lateral injuries, emotional, social, sexual, and/or physical disinhibition
	Inferolateral prefrontal cortex	Working memory	Impaired working memory
	Medial prefrontal (anterior cingulate) cortices	Motivation, sustained attention	Decreased goal-directed cognition, emotion, and behavior (ie, apathy)

Table IV. Continued.

medicine (and related disciplines) increases these challenges by focusing narrowly or emphasizing disproportionately one or another elements of the patient's presentation germane to (ie, within the more limited scope of practice of) each of these disciplines.

The information presented in the preceding sections of this article highlights the need for a transdisciplinary understanding of traumatic brain injury and its consequences, and calls for a neuropsychiatrically-informed, neurobiologically-anchored clinical approach. Our group suggested previously[6,22] that the pattern and course of clinical phenomena typical of the early post-injury period are usefully conceptualized as a post-traumatic encephalopathy. In the following section, it is suggested that this concept serves usefully as a foundation upon which to develop such an transdisciplinary clinical approach.

Definition of post-traumatic encephalopathy

Post-traumatic encephalopathy (PTE) denotes the clinical manifestations of brain dysfunction that develop immediately following application of an external physical force (including acceleration/deceleration and/or blast-related forces) to the brain. The term "encephalopathy" (meaning disorder or disease of the brain) captures the broad range of neuropsychiatric manifestations of neurotrauma-induced brain dysfunction and the term "post-traumatic" anchors the context of their occurrence to the post-injury period and their cause to TBI. Given that there is a broad differential diagnosis for event-related neuropsychiatric disturbances, this last point is especially important: proper use of the term PTE necessitates establishing with confidence that the encephalopathy represents neurotrauma-induced brain dysfunction and is not simply post-traumatic in that it occurs after trauma.

Taxonomically, PTE is superordinate to five linearly hierarchical subordinate stages (from lowest to highest): post-traumatic coma, post-traumatic delirium (confusional state), post-traumatic amnesia, and post-traumatic dysexecutive syndrome *(Table V)*. This organization is anchored to the most clinically salient cognitive feature of each stage of PTE, and describes the concurrent and/or persistent noncognitive neuropsychiatric symptoms of PTE at each stage as well.

Using PTE as a guide to the description, evaluation, and treatment of TBI-induced neuropsychiatric disturbances obviates the conceptual and semantic debate in this literature,[6-8,22,34,48,50,67-71] much of which derives from attempts to use any other single terms as a global descriptor of the clinical phenomenology of the post-injury period. The present framework acknowledges that the phenomena described by terms like "post-traumatic amnesia," "post-traumatic confusional state," and "post-traumatic delirium" may (and often do) occur after TBI and that each is a potentially important focus of clinical concern, study, and treatment. However, it encompasses all of these phenomena within PTE and regards each as only one of several stages through which persons with TBI transition during the post-injury period.

It would be conceptually correct to describe patients whose early post-traumatic neuropsychiatric disturbances become chronic problems as remaining in PTE (and the specific stage at which recovery reached its plateau). It is possible that there is merit to doing so, but the current practice is to describe such patients using more specific clinical descriptors. For example, wakefulness without awareness is usually described as a "vegetative state"[71] and wakefulness with minimal awareness is described as a "minimally conscious state."[70,72] It also is common to describe the clinical presentation of patients who fail to emerge from post-traumatic delirium or post-traumatic amnesia using the term "post-traumatic dementia" —that is, a syndrome of persistent and acquired impairments in multiple cognitive domains. Similarly, persistent mild cognitive impairments are often described as such, or instead as elements of post-concussional disorder or postconcussive syndrome[73-76]; we suggest that this may be an instance wherein post-traumatic dysexecutive syndrome may be both a useful and accurate term to describe these conditions. While the diagnostic terms presently in use are unlikely to be retired from clinical parlance at any point in the near future, it will be useful conceptually (and, perhaps, in TBI research endeavors) to regard their referents as specific subtypes of persistent PTE.

Finally, an additional advantage of this term is its semantic consistency with chronic traumatic encephalopathy,[77-79] a delayed-onset TBI-induced neurodegenerative disorder. Adopting a common semantic convention for the description of acute- and delayed-onset TBI-induced encephalopathies may facilitate the development of common clinical and research approaches to these problems, and further reduce the nosological confusion complicating such endeavors presently.

PTE stage	Salient (key) neuropsychiatric feature	Description	Additional features
Post-traumatic coma	Impaired arousal	Absence of arousal	No behavioral response to sensory input No spontaneous behavior (purposeful or non-purposeful) Preserved brain stem reflexes
Post-traumatic delirium	Impaired attention	Reduced clarity of awareness of the environment, as evidenced by a reduced ability to focus, sustain, or shift attention	Alterations of arousal Disturbances of sleep-wake cycle Motor restlessness Impaired processing speed, working memory, episodic memory (including orientation), language/communication, and executive function Perceptual disturbances (ie, illusions, hallucinations) Emotional lability Disinhibition, agitation, and/or aggression Fluctuation of the disturbance (not simply arousal, but the entire constellation of problems comprising delirium) Although other pre- or post-injury neuropsychiatric conditions may contribute to the above problems, the diagnosis of delirium generally precludes attributing these problems to another cause
Post-traumatic amnesia	Impaired episodic memory	Impaired declarative new learning, including orientation as well as autobiographical information for the peri- and immediate post-injury period	Impaired new learning is not attributable to lower-level cognitive impairments, including impaired arousal or selective and simple sustained attention Impaired processing speed (typically less severally impaired than during post-traumatic delirium) as well as higher-level (alternating, divided) attention, working memory, and executive function (including insight) are often present but less clinically salient than impaired episodic memory Emotional and behavioral disturbances may persist (eg, emotional lability, irritability, depression, anxiety, psychosis, apathy, aggression); these often represent the neuropsychiatric sequelae of focal injuries (ie, orbitofrontal syndrome) or damage to neurobehaviorally salient networks, other pre- or post-injury neuropsychiatric conditions, or some combination thereof
Post-traumatic dysexecutive syndrome	Executive dysfunction	Impaired intrinsic executive function (eg, conceptualization, judgment, insight) and impaired executive control of attention (ie, alternating, divided), working memory, declarative memory (ie, impaired retrieval), language, and/or motor planning	Emotional and behavioral disturbances may persist (eg, emotional lability, irritability, depression, anxiety, psychosis, apathy, aggression); these may continue to represent the neuropsychiatric sequelae of focal injuries (ie, orbitofrontal syndrome), damage to neurobehaviorally salient networks, other pre- or post-injury neuropsychiatric conditions, or some combination thereof

Table V. The stages of post-traumatic encephalopathy.

Neurobiological bases of post-traumatic encephalopathy

The stages of PTE described in this model are anchored to the regional vulnerability to TBI described in *Table III*. Post-traumatic coma reflects disturbances in the structure and function of upper brain stem and brain stem-diencephalic structures, including diffuse mechanically induced depolarization and synchronized discharge of cortical neurons, failure of ascending reticular activation system, or combinations of these and other processes.[59] These arousal-supporting systems often are the first to resume functioning after TBI, and their return to relative functional normalcy frequently precedes that of systems supporting selective and basic sustained attention; these latter systems include sensory cortical areas, the thalamic and subcortical areas to which they are connected, and white matter comprising not only those connections but also the ascending modulatory neurotransmitter systems that support them.[80]
Post-traumatic delirium (or post-traumatic confusional state) reflects restoration, although not necessarily complete normalization, of the function of neural systems serving arousal but continued dysfunction of those serving the most basic aspects of attention (and, by extension, higher cognitive functions as well).[7]
The function of the neural systems supporting basic attention tend to normalize prior to those supporting episodic memory, executive function, ie, anteromedial temporal and anterior frontal networks.[7,34,81] Dense impairments in declarative new learning (episodic memory) despite relative normalization of arousal and basic attention characterizes post-traumatic amnesia; during this stage of PTE, executive dysfunction also persists, but may be less clinically salient (even if functionally important) in the setting of dense anterograde amnesia.[34,81] The discrepancy between restoration of basic attention and more complex cognitive functions may be attributable, in part, to the relatively greater vulnerability of the temporal and frontal areas supporting memory and executive function to the effects of biomechanical forces, the cytotoxic cascade induced by biomechanical forces, the vulnerability of these systems to the effects of cholinergic and/or catecholamergic disturbances, or some combination of these and other factors.
Although the neurobiological bases of this recovery pattern require further investigation, the systems supporting episodic memory appear, in clinical practice, to resume functioning relatively normally prior to prefrontal systems—including those serving intrinsic executive functions, executive control of basic cognitive functions, comportment, and emotional regulation.[34,81,82] The persistence of these problems despite relative, though not necessarily complete, normalization of declarative new learning characterizes post-traumatic dysexecutive syndrome.
The clinical and neurobiological impairments that comprise each stage of PTE occur on a continuum and the transitions between these stages during recovery from TBI may not proceed unidirectionally: patients functioning cognitively at the transition point between stages of PTE may vacillate for days (or longer) between those stages. Nonetheless, identifying the stage of PTE that best describes that patient is useful in that it facilitates the development of a treatment plan that is appropriate to the patient's current clinical status. It also allows clinicians and the patient's family members to anticipate the course of continued recovery. By extension, this approach to PTE also helps clinicians to identify deviations from the expected course of recovery after TBI and to recognize the need to evaluate the patient for conditions that explain such deviations.

Recovery	Return to baseline cognitive function	Injury-related disturbances of cognition are no longer present or, if present, are attributable to another non-cognitive neuropsychiatric condition (eg, depression, anxiety, sleep disturbance, pain, medications, etc)	Non-cognitive neuropsychiatric symptoms, if present, may be attributable to injury-related factors, pre-injury factors, post-injury psychosocial factors, or interactions between them Irrespective of the attribution of subsequent neuropsychiatric symptoms to TBI and/or other issues, TBI remains relevant as a comorbidity that influences treatment selection and response expectations

Table V. Continued.

Evaluation of post-traumatic encephalopathy

The evaluation of PTE is predicated on a diagnosis of TBI using the clinical case definitions and initial injury severity descriptions reviewed earlier in this article. As noted above, consideration of the differential diagnosis for alterations of neuropsychiatric status in the post-injury period is also required, as is characterization of the neuroanatomy and, where possible, the neuropathophysiology of TBI. Even when the occurrence of TBI is incontrovertible, it will be necessary to entertain the possibility that a patient's encephalopathy reflects not only TBI but also co-occurring noncerebral injuries, medical conditions, and their interactions with other pre- or post-injury factors.

When it is clear that the patient is experiencing PTE, identifying the stage and severity of the encephalopathy is appropriate. The evaluation of PTE is facilitated by the use of measures that are designed to assess the key neuropsychiatric feature of each PTE stage. Although consensus is lacking on the optimal assessments of neuropsychiatric status during the post-injury period, expert panels, literature reviews, clinical research reports, and common clinical practice suggest that the measures presented in *Table VI* may be useful for this purpose.[6,8,10,23,81-108] In general, assessment of patients with these measures is performed serially (eg, daily for PTA assessments, at weekly or longer intervals for many other measures) during each stage of PTE. Since patients with more severe injuries are likely to experience protracted periods of PTE and since they often do not progress unidirectionally through its stages, it sometimes will be useful to administer measures relevant to two of these stages (eg, post-traumatic delirium and PTA, or PTA and post-traumatic dysexecutive syndrome) during the periods of transition between PTE stages.

Concurrently, performing a comprehensive neuropsychiatric assessment is recommended. This includes a detailed injury-event history; review of past and current medications, including those that may be contributing to neuropsychiatric disturbances or delaying recovery; identification of pre-injury developmental, medical, neurological, psychiatric, and substance use disorders; social history; family history, and general physical, neurological, and mental status examinations. On this latter point, the PTE stage-relevant assessments described in *Table VI* will be useful but do not constitute an adequate mental status examination. Direct, systematic, and repeated observation of the patient is often needed to identify intermittent or waxing and waning neuropsychiatric disturbances in this population, as are structured interviews of staff and family members about such issues. In this context, it also is essential to obtain from knowledgeable

PTE stage	Recommended assessments	Alternate assessments
Post-traumatic coma	Coma Recovery Scale – Revised (CRS-R)	Sensory Stimulation Assessment Measure (SSAM) Wessex Head Injury Matrix (WHIM) Western Neuro Sensory Stimulation Profile (WNSSP) Sensory Modality Assessment Technique (SMART) Disorders of Consciousness Scale (DOCS)
Post-traumatic delirium	Delirium Rating Scale-Revised-98 (DRS-R-98)	Confusion Assessment Protocol (CAP) Confusion Assessment Method (CAM) Cognitive Test for Delirium - Brief Inpatient version Delirium Diagnostic Tool – Provisional (DDT-Pro)
Post-traumatic amnesia	Orientation Log (O-Log) OR Galveston Orientation and Amnesia Test (GOAT)	Brief Inpatient Neuropsychological Battery Westmead PTA Scale Modified Westmead PTA Scale Oxford PTA Scale
Post-traumatic dysexecutive syndrome	Mini-Mental State Examination (w/Z-score) Clock Drawing Test (w/standardized scoring) Frontal Assessment Battery (w/Z-score) Neuropsychiatric Inventory	Executive Interview (EXIT 25) Neurobehavioral Rating Scale-Revised Brief Inpatient Neuropsychological Battery Formal neuropsychological assessment (typically if outpatient and ≥ 6 months post-injury)

Table VI. Assessment scales relevant to the examination of patients at various stages of post-traumatic encephalopathy. Abbreviations: PTE, post-traumatic encephalopathy; PTA, post-traumatic amnesia

informants a description of the patient's social history (eg, development, interpersonal style and habits, level of education, occupation and performance, legal history, military experience) and social supports (eg, marital status, family and friends). This information will identify strengths and limitations of the patient, the social context from which he or she hails, and the setting to which a return will be made after inpatient rehabilitation. This information may help patient, family, and health care providers anticipate likely long-term outcomes and community reintegration needs and to assess the financial resources (or lack thereof) available to support the rehabilitation process.

As suggested earlier, the correspondence between clinical phenomena and the neuropathophysiology upon which they are predicated is not absolute; there is substantial neurobiological heterogeneity within the diagnostic category of TBI. It therefore is important to characterize anatomic injury during the evaluation of persons in PTE. In many (perhaps most) cases in which TBI results in hospitalization, computed tomography (CT) of the brain will be performed in the acute injury setting. This imaging technology permits identification of skull fracture, acute hemorrhage, or hemorrhagic contusion, and very severe diffuse axonal injury, but is of limited value for more detailed characterization of neuroanatomic injury. Accordingly, we recommend obtaining magnetic resonance imaging (MRI) of the brain in all neurorehabilitation inpatients receiving neuropsychiatric assessment after TBI. T1-weighted, fluid-attenuated inversion recovery (FLAIR), T2*-weighted gradient echo, susceptibility-weighted (when available), and diffusion-weighted sequences should be included in MRI examinations of persons with TBI.[109] There is emerging evidence for the application of advanced neuroimaging technologies such as functional MRI, diffusion tensor imaging (DTI), magnetic resonance spectroscopy, cerebral blood flow (or metabolism) focused nuclear imaging, or neurotransmitter-targeted nuclear imaging (eg, positron emission tomography) to the evaluation of persons with a broad range of neuropsychiatric disturbances after TBI,[109] including those encompassed under the heading of PTE. At the present time, however, the usefulness of these technologies in the inpatient rehabilitation setting is uncertain; further research is needed to clarify the extent to which group-level findings reported in the literature obtain at the single-patient level.

Electroencephalography (EEG), including evoked potentials, event-related potentials, and quantitative EEG (qEEG), do not usually contribute usefully to the neuropsychiatric assessment of patients undergoing acute neurorehabilitation after TBI.[110] When clinical history suggests the possibility of seizures (particularly complex partial seizures with postictal confusion or behavioral disturbances), then it is appropriate to obtain an EEG to identify potentially epileptiform abnormalities. However, it is important to remain mindful that interictal EEG is relatively insensitive to epileptiform abnormalities and that the decision to treat patients for post-traumatic seizures rests on the event semiology and not on the presence or absence of electroencephalographic abnormalities.

The laboratory assessments evidence needed to guide in the acute neurorehabilitation setting also is underdeveloped. At a minimum, reviewing and/or obtaining laboratory data (including serum and urine studies) that may inform on contributors to, or alternate explanations for, encephalopathy after TBI is prudent. Recent reviews also suggest that neuroendocrine disturbances are common and underdiagnosed in this population.[111,112] Other than assessment of thyroid stimulating hormone and thyroid hormone levels, however, the best methods of assessing and treating other post-traumatic neuroendocrine disturbances remain matters of debate.

Treatment of PTE During rehabilitation after TBI

Perhaps the greatest challenge facing clinicians caring for persons with post-traumatic neuropsychiatric disturbances providing clinically useful interventions. There are many neurophysiologic processes involved in event-related alterations of consciousness and/or neurological function and, by extension, a broad array of potential neurobiological targets for neuropsychiatrically-directed post-TBI clinical interventions. Accordingly, there is a very low likelihood that any single intervention will attenuate the full complement of acute, and potentially chronic, neurobiological consequences of TBI.

For persons in PTE receiving inpatient rehabilitation, nursing care, treatment of medical issues, re-injury risk reduction (eg, fall prevention), and environmental/behavioral management are the cornerstones of treatment. In many patients, reducting or eliminating of medications that may interfere with neuropsychiatric function, rehabilitation, or recovery will be useful; for example, discontinuing anticonvulsants prescribed for

seizure prophylaxis among persons remaining seizure-free after the first week post-injury,[113,114] and avoiding use of typical antipsychotics and benzodiazepines.[36,115] There are published guidelines for these and related interventions in this population (see, for example, ref 113), including evidence-based analyses and systematic reviews of the types and potential benefits of various forms cognitive rehabilitation[116-118] and pharmacotherapies.[36,119-121] A comprehensive review of this literature is beyond the scope of this article, and readers are referred to the references cited here for more specific information on these subjects.

Regardless of the treatments prescribed for post-traumatic neuropsychiatric disturbances during the post-injury rehabilitation period, clinicians inevitably face the challenges of matching the treatments they provide to patients for whom they are likely to be most useful. The literature reviewed in this article suggests that there are several critical variables requiring consideration before prescribing rehabilitative interventions to persons with TBI: initial TBI severity, time post-injury (ie, as a reflection of the phase of the cytotoxic cascade), stage of PTE, and the specific neuropsychiatric treatment targets identified in these contexts.

Initial TBI severity influences the need for treatment and the focus of treatments offered. For example, the vast majority of persons with mild TBI require neither hospitalization nor formal neurorehabilitation and are likely to make a relatively rapid and full recovery without medical or rehabilitative interventions.[29,38] Indeed, the most effective interventions for this population are early support, education, and realistic expectation setting.[122,123] By contrast, the rate and extent of spontaneous recovery from TBI of moderate or greater severity is typically slower and long-term outcomes (even with rehabilitative interventions) often are less complete.[39,124,125] Those whose recoveries proceed to the point that they are effectively able to engage in rehabilitative interventions may benefit from rehabilitation, including various forms of cognitive rehabilitation, patient and family education, and support[116-118,123,126-128]; those whose deficits limit their direct engagement in such interventions may benefit more from family- or caregiver-directed training.[116-118]

The benefits or harms presented by a rehabilitative intervention, and especially pharmacotherapies, also are likely to vary with time post-injury. At the earliest time post-injury, the neurochemical excesses produced by cerebral neurotrauma may make the use of agents that augment cerebral neurotransmitter levels ineffective or neurochemically counterproductive.[121,129,130] By contrast, agents that attenuate the "neurotransmitter storm" might be therapeutically useful; for example, early intervention with amantadine, a moderate-affinity uncompetitive N-methyl-D-aspartate (NMDA) antagonist, appears to facilitate recovery of consciousness during the first week post-injury,[121] perhaps reflecting mitigation of early glutamate-mediated neurotoxicity. Although it might seem reasonable to hypothesize that antagonism other early post-injury neurotransmitter excesses toward this same end, the available evidence from clinical studies suggests that such interventions (eg, dopamine antagonism with haloperidol, use of agents with potent anticholinergic properties) are not only unhelpful but also may prolong PTE.[131-133]

The complexity of the neurochemical cascade makes the effects of such agents (or the lack thereof) difficult to anticipate,[134] but important to consider nonetheless. These issues might be more readily addressed by the application of in vivo imaging of neurotransmitter systems and/or other elements of the cytotoxic cascade; such imaging might identify specific elements of the cascade as targets for intervention or, perhaps more realistically, identify a point post-injury at which such treatments are likely to be safe and effective. The examples of such applications are promising[135] but remain underexplored in this field.

Presently, treatment may be organized most usefully by identifying the cognitive targets of treatment, the stage of PTE in which those targets occur, and (as a proxy marker for TBI neuropathophysiology) the time post-injury at which treatment is undertaken. As a general rule, medications that augment cholinergic function, catecholaminergic function, or both facilitate recovery of arousal, processing speed, attention, memory, and executive when administered during the post-acute rehabilitation period following TBI.[36,119,120] However, the cognitive effects of medications targeting these neurotransmitter systems are not identical: agents that augment cerebral catecholaminergic function appear to improve processing speed and, to a lesser extent, arousal and sustained attention (vigilance).[36,136] Agents that augment cerebral cholinergic function appear most useful for the treatment of declarative memory impairments and, among responders, may secondarily benefit other aspects of cognition.[36,137-139] These interventions are most

useful, in general, for persons who have progressed to or beyond the post-traumatic delirium stage of PTE; they do not appear to be particularly useful for persons in coma, vegetative states, or the minimally conscious state.[140]

Most of the medications used commonly in neurorehabilitative practices are mechanistically pleotropic. The several possible neurochemical effects of a given medication in the neurometabolic and neurochemical milieu into which it is introduced therefore are necessary considerations during treatment selection and will guide treatment response expectations. For example, early post-injury administration of uncompetitive NMDA receptor antagonists such as amantadine (or, perhaps, memantine) may attenuate the adverse effects of early glutamate excesses and facilitate progression from post-traumatic coma to higher stages of PTE. In the subacute or late post-injury period, the clinical benefits of amantadine[141] on post-traumatic disorders of consciousness (ie, vegetative or minimally conscious states after severe TBI) may reflect its NMDA receptor function-stabilizing properties, indirect facilitation of dopamine release by NMDA antagonism, other synapse-related effects on dopamine neurotransmission, or some combinations of these pharmacologic effects. When this same agent is used to treat the cognitive and other neuropsychiatric manifestations of the post-traumatic dysexecutive syndrome, especially after mild or moderate TBI, the beneficial effects of amantadine most likely reflect enhanced frontal function via indirect augmentation of cerebral dopaminergic activity.[36,119,120]

Zolpidem provides another example of the differential neuropsychiatric effects on a specific cognitive target based on the context (ie, initial injury severity, stage of PTE, time post-injury) in which it is administered. Zolpidem binds to $GABA_A$ receptors and thereby potentiates the effect of GABA, the principal inhibitory neurotransmitter in the central nervous system. Among persons with relatively intact arousal systems and minimal disturbances in other modulatory neurotransmitter systems (ie, persons in post-traumatic dysexecutive syndrome stage of PTE during the subacute or late post-injury periods following mild TBI), zolpidem is likely to impair arousal—hence its common use as an agent with which to treat insomnia. However, when administered to individuals with severely altered arousal and attentional systems in the subacute or late post-injury period following severe TBI (ie, persons with persistent post-traumatic disorders of consciousness), zolpidem may reciprocally disinhibit arousal systems among persons in the lower stages of PTE.[141,142] Whether this reflects a direct of effect of its action at $GABA_A$ receptors or a secondary effect of those actions on the function of other modulatory neurotransmitter systems remains uncertain. Whichever is the case, however, the context-dependent effects of this agent, as well as those of amantadine, highlight the need to consider not only the phenomenologic target of treatment but also the initial injury severity, stage of PTE, and time by post-injury (as a proxy for underlying neuropathophysiology) when prescribing medications to address neuropsychiatric disturbances during neurorehabilitation.

Initial TBI severity also may interact with other patient-specific factors, and particularly neurogenetics, in a manner that influences recovery course and treatment needs.[61,143,144] Genes that confer susceptibility to adverse outcomes—for example, the apolipoprotein ε4 allele—may interact with injury severity and/or age such that individuals of certain ages and injury severities with these genes may be a greater risk for poor outcome than those with other genetic characteristics.[145-147] Genes coding for enzymes that affect the metabolism of neurotransmitters involved in cognition also influence cognitive performance after TBI.[61,148] Since the neurotransmitter systems in which these genetic effects are expressed are potential targets of pharmacotherapies, treatment response expectations and/or medication dosing requirements might require modification based on patient-specific neurogenetics. Additionally, the influence of neurogenetics on treatment response or dosing requirements may vary with initial TBI severity and the state of the cytotoxic cascade during with treatment is offered, highlighting the need to entertain all of these factors whether one is treating an individual patient or designing a clinical trial.

In summary, the challenges of treating cognitive, emotional, behavioral, and sensorimotor—that is, neuropsychiatric—disturbances after TBI requires evolution of the manner in which clinicians match treatments to clinical problems. The considerations offered above suggest that the oft-used approach of treating "problem X" (ie, impaired sustained attention) with "medication Y" (ie, a stimulant or other catecholaminergic agent) is overly simplified in general and potentially hazardous during the early rehabilitation period after TBI more specifically. Rational pharmacotherapy of post-traumatic neu-

ropsychiatric disturbances during TBI neurorehabilitation requires consideration of not only the intended phenomenologic targets of treatment but also initial TBI severity, time post-injury (ie, phase of the cytoxic cascade), stage of PTE, and the influence and interactions between these factors.

Conclusion

The care provided to persons hospitalized following TBI is intrinsically and unavoidably neuropsychiatric: cognitive, emotional, behavioral, and sensorimotor (ie, neuropsychiatric) disturbances define TBI and remain the principal clinical manifestations of this condition throughout the post-injury period. These problems present substantial short- and long-term challenges to injured persons, their families, and the clinicians providing their care. In this article, a neuropsychiatrically informed, neurobiologically anchored approach to understanding and meeting challenges was outlined. That approach begins with the diagnostic evaluation, in which well accepted clinical case definitions are used and the differential diagnosis of TBI and injury event-related alterations in neuropsychiatric function are considered carefully. The influence of initial TBI severity and the neuropathophysiologies are considered with regard to the manner in which they inform on clinical presentation and course after TBI. The clinical manifestations of neurotrauma-induced brain dysfunction are then framed usefully as a PTE comprising several phenomenologically distinct stages. This framework guides clinical evaluation and treatment planning. In that context, the importance of considering initial TBI severity, time post-injury (ie, phase of the cytoxic cascade), stage of PTE, and the influence and interactions between these issues when selecting treatments for post-traumatic neuropsychiatric disturbances is evident.

If this approach to the challenges of neuropsychiatric disturbances during rehabilitation after TBI has merit, then it suggests several future research directions. First, research in this area must employ standard clinical case definitions of TBI and address the differential diagnoses, common comorbidities, and within-diagnosis heterogeneity of TBI. The Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health[1] is an example of the type of work needed to move the field toward this end. Second, research questions about clinical evaluations and interventions are most useful when they are predicated on robust a priori hypotheses anchored to the neuropathophysiology of TBI rather than to clinical phenomena alone is essential. Inferential reasoning about neuropathophysiology from the effects of pharmacotherapies is ill-advised: ie, concluding that since an agent that augments the levels of a given neurotransmitter, and since administration of that agent appears to improve cognition after TBI, then TBI must produce deficits of that neurotransmitter. The effects of "selective" or "neurotransmitter-specific" medications are rarely as specific as purported, and some agents (eg, stimulants, cholinesterase inhibitors, selective serotonin reuptake inhibitors) sometimes improve neuropsychiatric (and especially cognitive) function among healthy individuals. Advances in our understanding of the neuropathobiology of TBI may yield reliable neuroimaging markers, biomarkers, or other indices that facilitate the development of neurobiologically rational, effective, and potentially neuroprotective or neurorestorative interventions. Additional attention to patient-specific factors such as neurogenetic factors may contribute usefully to the development of such interventions as well.

Ideally, research and clinical efforts in this area will integrate clinical assessments (for example, those informed by the framework of PTE presented here) with advanced neuroimaging, neurogenetics, and other biometrics to better match interventions studied and deployed to the people to who they are provided. Multicenter randomized controlled trials guided by this type of integrated clinical, neurobiological, and patient-centered research approach will better define optimal methods for addressing the neurorehabilitative challenges presented by post-traumatic neuropsychiatric disturbances. ❑

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Enfocándose en las alteraciones neuropsiquiátricas durante la rehabilitación post daño cerebral traumático: métodos actuales y futuros

Las alteraciones cognitivas, emocionales, conductuales y sensoriomotoras son las manifestaciones clínicas principales del daño cerebral traumático (DCT) durante el período inicial post lesión. Estas alteraciones neuropsiquiátricas postraumáticas presentan importantes desafíos para los pacientes, sus familias y los médicos a cargo del tratamiento durante la rehabilitación, y no se ha desarrollado en forma completa un abordaje óptimo. En este artículo se describe un abordaje con información neuropsiquiátrica y soporte neurobiológico para comprender y enfrentar los desafíos. El fundamento para este abordaje se presenta con una revisión de las definiciones del caso clínico de DCT y una clarificación de sus términos propuestos. A continuación se considera el diagnóstico diferencial de las alteraciones neuropsiquiátricas relacionadas con el acontecimiento y luego se discute la heterogeneidad clínica y neurobiológica de las categorías diagnósticas del DCT. Las manifestaciones clínicas de la disfunción cerebral inducida por una fuerza biomecánica se describen como un estado de encefalopatía postraumática (EPT) que incluye algunas etapas específicas fenomenológicamente. Por lo tanto la EPT se emplea como un marco para la comprensión y evaluación clínica de las secuelas neuropsiquiátricas del DCT que aparecen comúnmente durante el período inicial de la rehabilitación post lesión, y para tener en cuenta de los tipos y tiempos de las intervenciones de neuro-rehabilitación. Por último, se consideran las orientaciones para futuras investigaciones que puedan abordar de manera productiva los desafíos que presentan las alteraciones neuropsiquiátricas para la rehabilitación del DCT.

Évaluation des troubles neuropsychiatriques pendant la réadaptation après lésion cérébrale traumatique : méthodes actuelles et futures

Les troubles cognitifs, émotionnels, comportementaux et sensorimoteurs sont les principales manifestations cliniques des lésions cérébrales traumatiques (LCT) au cours de la période post-traumatique précoce. Ces troubles neuropsychiatriques post-traumatiques représentent un véritable défi pour les patients, leur famille et les médecins qui prodiguent leurs soins de réadaptation, et dont les méthodes restent imparfaites. Nous décrivons dans cet article une approche neuropsychiatrique, sous-tendue par la neurobiologie, permettant la compréhension et la réalisation d'objectifs. Les fondements de cette approche reposent sur une revue des définitions des cas cliniques des LCT et sur une clarification de leur origine. Nous examinons ensuite le diagnostic différentiel des troubles neuropsychiatriques liés à ces événements, puis nous analysons l'hétérogénéité clinique et neurobiologique de la catégorie diagnostique des LCT. Les manifestations cliniques des troubles cérébraux induits par la force biomécanique sont décrites comme un état d'encéphalopathie post-traumatique (EPT) comprenant plusieurs stades distincts sur le plan phénoménologique. L'EPT est alors utilisée comme cadre de compréhension et d'évaluation clinique des séquelles neuropsychiatriques des LCT rencontrées habituellement pendant la période de réadaptation post-traumatique précoce, renseignant sur les types et la chronologie des interventions de réadaptation neurologiques à adapter. Les directions à prendre pour la recherche future sont envisagées, afin d'aborder de façon productive les défis de la réadaptation aux LCT liés aux troubles neuropsychiatriques.

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