The Agitated Brain Injured Patient. Part 2: Pathophysiology and Treatment

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The management of agitation after brain injury remains uncertain because of a lack of a consistent definition and a poor understanding of the underlying mechanism. Part 1 of this review focused on definitions, differential diagnosis, and assessment. Part 2 reviews potential mechanisms for posttraumatic agitation and common intervention strategies. The intent of this two-part series is to advocate for a consistent definition for posttraumatic agitation, to encourage the use of appropriate assessment and monitoring strategies, and to recommend that intervention decisions are based on at least a theoretical understanding of the relationship between specific target behaviors and probable brain-behavior relationships.

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POSTTRAUMATIC AGITATION represents a highly disruptive and potentially unsafe behavior that is observed in 33% to 50% of acute coma-emerging traumatic brain injury (TBI) survivors.1 The significance of posttraumatic agitation is additionally underscored by the observation that it may be predictive of residual behavioral disturbances.2 Despite the frequency of this sequela of severe TBI, the definition has been inconsistent, the pathophysiology remains unclear, and effective interventions are unproven. In Part 1, we proposed the following definition for this clinical disorder: posttraumatic agitation is a subtype of delirium, occurring during the period of posttraumatic amnesia, that is characterized by excesses of behaviors, including some combination of aggression, akathisia, disinhibition, and emotional lability.3 This definition structures the discussion that follows. Specifically, this discussion reviews the common pharmacologic and nonpharmacologic treatment options for posttraumatic agitation. This article also discusses potential pathophysiologic mechanisms of posttraumatic agitation with the intent to support the rationale for common treatment strategies.

The electronic database Medline was utilized in an effort to comprehensively screen the available literature. The information in this article represents information available as of July 1995. Key words included brain injury, brain trauma, head injury, head trauma, and delirium. These key words were then crossed with each of the neurotransmitters and the pharmacologic agents described in this manuscript. This process generated an excess of 3,000 abstracts and 150 manuscripts that formed the basis for Part 2 of this series.

NEUROPATHOLOGY OF TBI

The study of brain-behavior relationships is based on the assumption that complex human behavior is dependent on physiological processes within the central nervous system. Therefore, observed behavior should correlate with anatomic, physiological, or neurochemical processes within the brain. However, TBI often represents the combined effects of discrete, diffuse axonal, ischemic, or anoxic injuries. The common sites of focal brain injury after trauma are the anterior and orbito-frontal cortices and the anteriomedial and inferior temporal cortices. Additional diffuse axonal injuries are described affecting connecting pathways, such as the corpus callosum, cortical-subcortical systems, or brain stem-cortical systems.4 The heterogeneity of these brain injury mechanisms after trauma renders brain-behavior correlations difficult.

Given the current state of knowledge, we must conclude that agitation has no clearly defined pathophysiologic substrate to distinguish it from other neurobehavioral consequences of TBI. For example, in one study the observation that aphasic patients were more likely to be agitated than nonaphasic patients did not correlate with computed tomography (CT) studies.5 Despite a dearth of research on the pathophysiologic substrate for posttraumatic agitation, clinically relevant information might be drawn from available information regarding the pathophysiology of (1) coma-emerging states and delirium, (2) the characteristic impairments in cognition after TBI (attention and memory), and (3) the characteristic behaviors of posttraumatic agitation (aggression, akathisia, disinhibition, and emotional lability).

Coma-emerging states. Several studies and observations support the importance of structural and organizational disruption to the phenomenon of agitation during the coma-emerging period. Frontal cortical cerebral blood flow has been shown to be reduced relative to subcortical and posterior structures in patients during coma.6 Blood flow patterns then normalize as patients become responsive, but the relevance of this observation to the subsequent development of cognitive or behavioral disturbances is uncertain. Damage to interconnections between the frontal cortex and subcortical nuclei in the striatum, globus pallidus, substantia nigra, and thalamus may also contribute to agitation as these structures mediate complex attentional abilities, executive functions, and emotional aspects of both arousal and awareness.7 Ommaya and Gennarelli8 additionally observed that the hippocampal mesocortical and temporal mesocortex "bear the brunt of the cortical damage," perhaps explaining the impaired arousal that precedes recovery from both agitation and other cognitive impairments after brain injury.

Delirium. A number of studies involving stroke patients have linked infarction in the right middle cerebral artery territory to acute agitated delirium.9-11 In patients with cerebrovascular infarcts, two states that are similar to post-traumatic agitation...
have been described: (1) an acute confusional state, with cognitive deficits only, and (2) acute agitated delirium, with inattention, autonomic hyperactivity, restlessness, irritability, and possible delusions and hallucinations. The acute confusional states after right brain injury have been linked to lesions involving the parietal lobe and frontosubcortical regions, the middle temporal gyrus, the hippocampal formation, and the fusiform gyri of the medial temporal lobe.

**Attentional disorders.** Injury to the reticular activating system of the brain stem produces impairments in arousal and alertness and may contribute to agitation. However, it appears to be unlikely that brain stem injury alone produces agitation, because isolated brain stem disorders are not associated with either delirium or agitation. Isolated brain stem injury was documented after mild brain injury in one animal study, but after a severe TBI, brain stem injury is associated with extensive cortical injury.

**Memory disorders.** Global anterograde amnesia has been described (1) after bilateral surgical destruction of the anterior two thirds of the hippocampus and hippocampal gyrus, the uncus, and the amygdala, with sparing of the lateral neocortex, (2) in Korsakoff’s disease (medial diencephalic lesions), (3) after rupture of the anterior communicating artery (prefrontal cortex injury), and (4) in Alzheimer’s disease. Hippocampal damage with evidence of memory deficits has been documented after mild brain injury in nonhuman primates, suggesting a similar neuropathologic substrate (temporo-limbic systems) for posttraumatic amnesia after less severe injuries.

**Akathisia and aggression.** Akathisia was defined in Part 1 of this review as a compulsion to move about, resulting in an inability to remain seated. Akathisia has been associated with the adverse effects of neuroleptics. Parkinson’s syndrome, idiopathic Parkinson’s Disease, and other basal ganglia lesions.

The pathogenesis is postulated to be a competitive blockade of mesocortical postsynaptic dopamine receptors. Descriptions of akathisia such as motor restlessness and aggression are similar to behaviors observed in posttraumatic agitation, suggesting a common neuropathogenesis.

**Disinhibition and emotional lability.** Disinhibition and emotional lability are clearly associated with orbitofrontal injury. The orbital regions are reciprocally connected with the dorsomedial nucleus of the thalamus and the amygdala, structures associated with memory functions. The frontal limbic cortex is located in the cingulate gyrus on the medial aspect of the frontal lobe, and is connected to the amygdala, anterior thalamus, and septum. Lesions in this region are observed after mild as well as severe brain injury causing a divorce of frontal monitoring systems from limbic input, thereby resulting in disinhibited, socially inappropriate behaviors and emotional lability.

**Conclusion.** Injuries to fronto-temporal systems (and possibly related subcortical and brainstem regions) which subserves arousal, attention, memory and limbic behavioral functions are likely pathologic substrates for the development of posttraumatic agitation. Given the diverse characteristic behavioral and cognitive components of agitation, the possibility that agitation represents the consequence of the combined effects of more than one lesion must be considered. More research is necessary to establish the precise localization of neurophysiological disturbances within these anatomic systems.

**NEUROTRANSMITTERS**

Neural chemicals may hold the key to understanding the behavioral effects of TBI and subsequently offer insight into the most efficacious pharmacologic strategies. Unfortunately, clinical trials have focused primarily on the very acute phase after injury occurring within hours of trauma, with little subsquent understanding of the clinical relevance of subacute or chronic derangements of neurotransmitter systems. An understanding of derangements of neurotransmitter systems may explain the evolution in behavior and cognition seen as patients emerge from coma into an agitated state and assist in determining appropriate pharmacologic strategies for patients.

**Catecholamines.** Noradrenaline, epinephrine, and dopamine all belong to a class of compounds known as catecholamines. The dopamine projections relevant to this discussion include those projections from the ventral tegmental and substantia nigra cells that project to the neostriatum and the limbic system. Noradrenaline cell bodies are primarily clustered within the caudal pontine area referred to as the locus coeruleus and the lateral tegmental regions. Effetive noradrenergic pathways project to the cerebellum and hippocampus, and diffusely through the cerebral cortex. Adrenergic neurons within the central nervous system are largely intermingled with noradrenergic cells. Catecholamines have significant roles in learning, memory, motivation, sleep-wake cycle regulation, and arousal.

Dopamine and noradrenaline also appear to be important neurotransmitters in recovery from brain injury. Studies have documented early, profound alterations in catecholamines after brain injury, with subsequent prognostic and recovery implications. Clinical evidence exists that cerebrospinal fluid levels of catecholamines are diminished in agitated brain injury survivors. Interventions that enhance central nervous system catecholamines hold significant promise for accelerating recovery during the coma-emerging stage and diminishing the period of agitation. The importance of catecholamine systems in recovery after brain injury in human subjects has in fact been supported by a number of clinical studies and case reports. The medications employed in these studies have included dextroamphetamine, methylphenidate, amantadine, bromocriptine, levodopa-carbidopa, and tricyclic antidepressants.

**Serotonin.** The pontomesencephalic brain stem provides serotonergic innervations to both the cortex and thalamus. Serotonergic pathways originate from the nuclei of the midline raphe, and efferent neurons subsequently project widely throughout the central nervous system, including the limbic system, neostriatum, cerebral, and cerebellar cortices and the thalamus. Serotonin is implicated in a variety of physiologic, affective, and cognitive functions ranging from modulating pain, sleep and arousal, cardiac function, memory, mood, aggression, anxiety, eating behavior, and addictive behavior. Cognitive effects attributed to serotonin include mediating arousal and enhancing both memory and learning. Memory-enhancing serotonin receptor antagonists appear to have preferential affinity for 5-HT1 and 5-HT2 receptor sites. A considerable body of literature exists describing the relationship of serotonin in the regulation of mood and behavior. Evidence supports serotonin levels as the most significant predictor of aggressive behavior compared to other genetic, hormonal, neurochemical, substance abuse, or psychiatric factors. Specifically, low cerebral spinal fluid levels of 5-hydroxyindole-acetic acid are consistently linked with impulsive, aggressive, violent, and destructive behaviors. This may be an important issue in TBI, as data have shown that agitated TBI survivors have lower levels of serotonin in cerebral spinal fluid than nonagitated survivors.

**Acetylcholine.** The basal forebrain cholinergic complex includes the septal nuclei, nucleus of the diagonal band, and nucleus basalis of Meynert. Neurons projecting from the basal forebrain project to the entire cortical surface. A second subconstellation of cholinergic neurons arise from the pontomesencephalotegmental cholinergic complex of pedunculopontine and laterodorsal tegmental nuclei. These project to the thalamus, the reticular formation,
cerebellum, and vestibular nuclei. Cholinergic neurons play prominent roles in sleep onset and maintenance and normal regulation of cognition and behavior. Evidence supporting the role of cholinergic neurons projecting from the basal forebrain in memory include the observation that scopolamine, a central acting anticholinergic agent, induces an amnestic state in rats. Additionally, the selective loss of neurons in the nucleus basalis of Meynart in Alzheimer’s disease supports the “cholinergic hypothesis of memory.” However, studies exploring the efficacy of acetylcholine replacement for memory enhancement have been disappointing. Acetylcholine additionally appears to play a prominent role in the mediation of arousal through the ascending reticular formation and through enhancing the responsiveness of neurons to sensory input. The importance of acetylcholine in the regulation of mood has been advanced through an “adrenergic-cholinergic imbalance hypothesis of depression.” This hypothesis posits that the cholinergic-adrenergic balance is involved in the regulation of drive and mood. Anticholinergic agents are frequent causative factors in the development of delirium. On the other hand, anticholinergic treatment may enhance outcome because the cholinergic system has been implicated in modulating a number of pathophysiological sequelae of TBI in the acute period after injury.

Conclusion. Neurochemical deficiencies or dysregulation may be the neurophysiologic basis for posttraumatic agitation. Unfortunately, no human studies have attempted to correlate brain structure with subsequent neurochemical alterations in this subacute phase. Most likely, disruption of a number of neurotransmitter systems, in particular the dopaminergic and noradrenergic systems (arousal and attention) and cholinergic systems (memory), result in the cognitive effects characteristic of agitation. The behavioral effects may result from effects on serotonergic systems (aggression), dopaminergic systems (akathisia), or combinations of effects on a variety of neurotransmitter systems (disinhibition and emotional lability). Finally, it is important to recognize that neurotransmitter systems are complex systems that do not function in isolation; rather, human behavior, such as agitation, is more likely to result from abnormal neurotransmitter interactions.

TREATMENT

A systematic evaluation of the coma-emerging patient is the obvious first step for the optimal treatment of secondary behavioral disorders. Ideally, the target behaviors of posttraumatic agitation should be divided into those that are most amenable to nonpharmacologic intervention versus those that require or optimally respond to psychopharmacologic intervention. That type of distinction is not possible given today’s body of research. Although unproven, it is logical to assume that the most effective intervention for posttraumatic agitation would combine both pharmacologic and nonpharmacologic strategies. This section will review those common strategies that are described as effective in the treatment of posttraumatic agitation. However, it is important to understand the limitations of much of this literature in that it is largely based on animal studies or studies exploring the treatment of target behaviors in a variety of other clinical disorders (psychiatric populations, organic brain syndrome, dementia, etc.) with results that may not be entirely appropriate to generalize to posttraumatic agitation.

Behavioral Intervention

Two broad types of behavioral techniques have been effective in the management of TBI survivors: response-consequence learning and stimulus-control learning. The stimulus-control learning procedure attempts to change behavior by manipulating antecedent events. This technique relies on the patient’s ability to discriminate those aspects of the environment that act as cues for an undesirable behavior. Therefore, the patient is asked to recognize and respond to those signals with more socially appropriate behaviors. Response-consequence learning focuses on the association between the behavior and its subsequent consequences. An example of response-consequence technique is the time-out method. A token economy is yet another example of response-consequence learning that involves identifying target behaviors to be increased and constructing contingencies that specify the number of tokens received for each target behavior.

Both response-consequence learning and stimulus-control techniques are dependent on associational learning. For the coma-emerging patient with significant posttraumatic agitation, this type of learning is frequently profoundly impaired. Under these circumstances, a structured milieu that is consistent, provides an assortment of productive activities, and minimizes excessive sensory stimulation is the more commonly utilized, nonpharmacologic behavioral intervention. The acutely agitated brain injury survivor occasionally responds to de-escalation techniques, but verbal de-escalation of aggression is rarely effective with psychotic or organic brain syndrome patients.

Restraints or seclusion represent controversial forms of emergency, nonpharmacologic interventions for acutely violent, agitated survivors. Both of these techniques warrant close supervision by nursing staff and frequent evaluations by the medical staff. Institutional guidelines typically outline indications for restraints or seclusion, supervision requirements, and mandates that authorizing orders are time limited. Additionally, these guidelines typically mandate that orders for a restraint or seclusion must be reviewed and renewed periodically.

Pharmacologic Intervention

The role of pharmacologic interventions for the behavioral sequelae of TBI is likely to increase in importance. This observation is based on advances in the neurosciences that indicate appropriately timed pharmacologic interventions improve outcome. Also, the considerable time and staff requirements for behavioral interventions together with the increasing pressure to shorten inpatient rehabilitation have diminished the role of behavioral strategies for the neurobehavioral sequelae of TBI.

A recent survey of rehabilitation professionals involved in the care of TBI survivors explored the number of clinical approaches utilized in the management of agitation after TBI. In decreasing order, the pharmacologic agents most commonly used in the management of posttraumatic agitation included carbamazepine, tricyclic antidepressants, beta-blockers, haloperidol, benzodiazepines, methylphenidate, buspirone, trazodone, and amantadine. The intent of this section is to review primarily these pharmacologic agents regarding their relative merits and limitations in the management of posttraumatic agitation.

Carbamazepine. Carbamazepine is an iminodiabenzyldrug that is erratically absorbed from the gastrointestinal tract. The anticonvulsant properties of carbamazepine are thought to be mediated through benzodiazepine receptors, a2-adrenergic receptors and or stabilization of sodium channels on neurons. Carbamazepine may be indicated in the treatment of manic disorders, bipolar disorders, schizoaffective disorders, depression, and a variety of impulse-control disorders including aggression. Clinical evidence from patients with seizure disorders also suggests that carbamazepine has anxiolytic properties.

A nonrandomized, placebo-controlled, crossover trial study documented that low doses of carbamazepine reduce agitation behaviors in a nursing home population. Antiaggression properties of carbamazepine also have been documented in patients...
with episodic violence secondary to personality disorders or mental retardation. Additionally, case studies have documented the effectiveness of carbamazepine in the management of agitation and aggression after acute brain injury.

Adverse effects of carbamazepine include blood dyscrasias, hepatitis, Stevens-Johnson Syndrome of exfoliative dermatitis, gastrointestinal distress, and central nervous system effects. The central nervous system adverse effects most relevant to TBI survivors include disorders of balance and sedation. Carbamazepine is considered to be relatively free of cognitive adverse effects when compared to other anticonvulsives. The most prominent observed negative effects on cognitive performance associated with carbamazepine include those requiring motor and speed skills such as reaction time and visuomotor speed.

The desired behavioral effects attributed to carbamazepine do not require “therapeutic” doses of carbamazepine. The ag- gestion-inhibiting properties of carbamazepine have been noted in doses of approximately 300 to 400mg per day. This observation, however, is based on studies involving elderly demented patients and anecdotal evidence in TBI survivors. Despite the reported propensity for rehabilitation professionals to utilize carbamazepine in the management of posttraumatic agitation, there are no controlled studies evaluating the efficacy of this intervention in the management of posttraumatic agitation.

Antidepressants. The antidepressants are comprised of several broad categories of pharmacologic agents that include serotonin-specific reuptake inhibitors, tricyclic antidepressants, tetracyclic antidepressants, and a fairly unique antidepressant, trazodone. Trazodone functions primarily as a serotonin reuptake inhibitor but its adverse effects are partially mediated by alpha-adrenergic antagonism and antihistaminergic activity. The serotonin-specific reuptake inhibitors are highly specific, with indirect effects on norepinephrine, acetylcholine, or dopamine neurotransmission. The tricyclic and tetracyclic antidepressants block the reuptake of both norepinephrine and serotonin and block both muscarinic acetylcholine receptors and histamine receptors.

In addition to the treatment of depression, the antidepressants have been advocated as effective in treating panic disorders, generalized anxiety disorders, obsessive compulsive disorders, eating disorders, pain, and sleep disturbances. The antidepressants have been used in the management of posttraumatic agitation. In one series of 17 patients, amitriptyline dramatically decreased agitation in 12 of the 17 patients within 7 days of initiating that intervention. Amitriptyline appeared to be more useful as an adjunct in the treatment of undirected agitation. The optimal therapeutic dose of amitriptyline for the management of posttraumatic agitation rarely exceeded 75mg per day.

The anticholinergic properties of tricyclic and tetracyclic antidepressants are potentially problematic in that anticholinergics are the most common category of medications that induce delirium. Interestingly, the sedation commonly associated with tricyclic antidepressants and trazodone does not appear to interfere with the management of posttraumatic agitation. Trazodone is rarely associated with the occurrence of priapism. Potentially problematic adverse effects associated with serotonin-specific reuptake inhibitors include anxiety, sexual dysfunction, excessive weight loss, and the serotonin syndrome. Finally, a number of antidepressants are associated with lowering seizure threshold.

Trazodone appears to be the most commonly utilized serotoninergic agent for the management of agitation. Trazodone has been used effectively to decrease agitation in patients with dementia and organic brain syndrome. One series described several cases in which trazodone was effective in ameliorating agitation, even after a number of other antidepressants had apparently failed. Therapeutic doses of trazodone for the management of agitation appear to range widely between 25 to 400mg per day.
The major indication for sympathomimetic agents is in the treatment of attention deficit disorder and narcolepsy. These agents have been effectively utilized in the treatment of depression when the depression has failed to respond to more traditional interventions. Additionally, the sympathomimetic agents appear to provide a safe and effective alternative in the management of depression in populations with concurrent medical illness.

Sympathomimetic agents have been used as pharmacologic adjuncts in the management of TBI survivors. Cases have been reported in which the sympathomimetic agents improved arousal, improved cognitive function, and decreased the number of the neurobehavioral sequelae in nonagitated survivors of TBI. In addition, methylphenidate is among the most frequently used pharmacologic agents to treat posttraumatic agitation by rehabilitation professionals.

The adverse effects associated with sympathomimetic agents include anxiety, irritability, agitation, anorexia, and psychosis, and they may lower seizure threshold. The use of sympathomimetic agents for non-FDA-approved indications is controversial because these agents are considered to possess considerable abuse potential.

Methylphenidate doses typically range between 10 and 60mg per day. Dextroamphetamine doses range between 2.5 and 40mg per day. These medications are frequently administered at 8:00AM and 12 noon to maximize their efficacy and minimize secondary insomnia.

**Buspirone.** Buspirone is a novel anxiolytic drug that has been effectively utilized in the management of TBI survivors. Unlike the benzodiazepines, buspirone does not appear to act on GABA receptors; instead, the behavioral effects of buspirone appear to be associated with its 5-HT, receptor activities. Buspirone’s primary indication is in the management of generalized anxiety disorder. Buspirone has also been utilized in the management of obsessive compulsive disorder, posttraumatic stress disorder, and as an adjunct in the treatment of depression. Additionally, buspirone has been effectively utilized to decrease self-injurious behavior in individuals with mental retardation, organic-induced agitation, and post-traumatic agitation.

Buspirone does not appear to cause significant sedation. There is no known addiction potential, and no significant adverse cognitive effects appear to be attributable to buspirone. The maximum dosage of buspirone is 60mg per day but several cases describe the safe utilization of doses as high as 180mg per day. The primary disadvantage of buspirone is related to the delay in therapeutic action attributed to this pharmacologic agent. This delay has been reported to range between 5 days to 12 weeks.

**Amantadine.** Amantadine augments dopaminergic neurotransmission in the nervous system and appears to function as a N-methyl-D-aspartate receptor antagonist with neuroprotective properties. The primary indication for amantadine is in the treatment of extrapyramidal symptoms. Amantadine is also used in the prevention and treatment of influenza type A infections. Amantadine has been demonstrated as effective in the treatment of fatigue associated with multiple sclerosis and in decreasing depression. In populations with dementia, amantadine appears to decrease perseveration, improve arousal, and improve cognition. Amantadine for TBI survivors may be efficacious in improving attention, arousal, processing time, psychomotor speed, mobility, vocalization, anxiety, motivation, and agitation.

Adverse effects include irritability, depression, anxiety, and ataxia; these have been reported to occur in approximately 20% of patients. Less frequent but severe adverse effects include
coma, ventricular ectopy, tics, de pointes, exacerbation of schizophrenia, recurrent neuroleptic malignant syndrome, toxic delirium, and mania. Despite the seriousness of these potential adverse effects, amantadine is well tolerated with starting doses of 100 mg twice per day and maximum doses of up to 400 mg per day. The therapeutic effects of amantadine are typically noted within several days.

**Lithium.** Lithium is infrequently used in the management of posttraumatic agitation by rehabilitation professionals. Nevertheless, this is an important psychoactive agent worthy of brief description. The therapeutic mechanism for lithium remains uncertain. It is typically indicated in the management of bipolar disorder, but it has additionally been used in the treatment of schizoaffective disorders, major depression, schizophrenia, and various types of impulse-control disorders.

The use of lithium for the management of impulse-control disorders such as episodic violence and rage have led investigators to conclude that this is a potentially important intervention for posttraumatic agitation. Several reports describe lithium as effective in the treatment of bipolar disorders following TBI. In 1985, a single case report indicated that lithium was effective in decreasing posttraumatic agitation after other psychoactive agents failed. Subsequently, a series of 10 agitated brain injury survivors were treated with lithium and agitation improved in 7 patients, the other 3 patients developed neurotoxic adverse effects.

Potentially serious toxic effects of lithium warrant close monitoring of lithium levels. Neurologic manifestations of toxicity include visual changes, disorders of movement, seizures, syncope, stupor, coma, and delirium. Other potential adverse effects of lithium that necessitate close monitoring include renal impairment, hypothyroidism, ventricular arrhythmias, and delirium.

The psychiatric literature suggests that the typical starting dose of lithium for most adults is 300 mg three times daily, lower starting doses may be appropriate for agitated brain injury survivors. Therapeutic levels of lithium for psychiatric illness are considered to be 0.8 to 1.2 mEq/L, whereas maintenance levels of lithium range between 0.6 and 0.8 mEq/L. Adherence to those therapeutic levels does not appear to be necessary in the management of posttraumatic agitation.

**Valproic acid.** Valproic acid is a carboxylic acid that increases brain levels of GABA through inhibition of catabolism, activation of synthesis, and enhancement of postsynaptic effects. Valproic acid indications include the management of seizure disorders, psychosis from schizophrenia, mania, bipolar disorders, depression, vascular headaches, and drug-induced akathisia.

Valproic acid also has been effectively used in the management of agitation with aggression resulting from a variety of clinical disorders. These would include bipolar disorders, borderline personality disorders, and dementia. Despite these observations, the previously mentioned survey describing treatment tendencies of TBI rehabilitation professionals failed to include valproic acid.

The more significant adverse effects of valproic acid include gastrointestinal discomfort, thrombocytopenia, liver disorders including hepatitis, pancreatitis, ataxia, headaches, anxiety, and depression. Sedation and the gastrointestinal discomfort are usually transient. Valproic acid may potentiate the effect of coumadin.

The adverse effects of valproic acid may be minimized with starting doses of approximately 250 mg per day. Therapeutic plasma levels of 50 to 100 mg/mL typically require total daily doses of 1,000 to 1,500 mg. The utilization of valproic acid for the management of agitation is adjusted on the basis of clinical response rather than "therapeutic" levels.

**Conclusion.** Final recommendations for the pharmacologic treatment of choice for posttraumatic agitation are not given because of the disturbing lack of well-controlled clinical trials necessary to make such recommendations; consequently, there is no FDA-approved drug for the management of agitation. Also, posttraumatic agitation may not have a single underlying neuropsychiatric mechanism; therefore, future studies are likely to demonstrate that specific target behaviors of posttraumatic agitation respond differentially to various pharmacologic agents.

Finally, the failure of patients to respond to the above described pharmacologic interventions may represent the consequence of adverse drug reactions. Studies have shown that a decline in cognition during posttraumatic agitation is often due to adverse drug effects and that cognition must improve before agitation resolves. Hence, should agitation not resolve in a timely fashion, an interruption of all pharmacologic intervention warrants consideration.

**References**
