Clinical Vignette

MH is a 47-year-old man who was prescribed phenelzine, a monoamine oxidase inhibitor (MAOI), for depression. He presented to the emergency department with sudden onset of “the worst headache of his life.” He frequently took caffeine pills, including, on the day of presentation. His initial exam was notable for lack of focal neurologic deficits, but he declined clinically soon after with confusion, urinary incontinence, and left hemiparesis with a National Institutes of Health Stroke Scale score of 19. Computed tomography (CT) of his brain demonstrated a large right basal ganglia hemorrhage (8 cm x 3 cm, approximately 70 mL) with extension into the ventricles, frontal lobe, and medial temporal lobe (See Image 1). Angiography was notable for lack of vascular abnormality, and follow-up imaging demonstrated a stable hematoma with increased cerebral edema and midline shift approaching 1 cm. He did not improve, and on the third hospital day underwent decompressive hemicraniectomy with hematoma evacuation. He was extubated on day five and subsequently began to hallucinate, insisting his wife or others were in the room when they were not. On day 10, he was transferred to the UPMC Physical Medicine and Rehabilitation Acquired Brain Injury service.
Upon admission to inpatient rehabilitation (IPR), he perseverated on his history of severe depression and insisted on restarting phenelzine. His language was fluent with mild naming deficits and intact repetition, along with good orientation, comprehension, and abstraction. A motor exam was notable for dense left hemiplegia with left neglect and profound anosognosia. Over the next several days, ongoing hallucinations, emotional lability, headache, and a low frustration threshold led to vigorous refusal of his daily care routines. He refused to use his craniectomy helmet, was unwilling to get out of bed, and had sudden outbursts of verbal and physical aggression, from cursing to throwing his helmet to breaking a bedside table. His family asked if anything further could be done to help him.

**Epidemiology and Common Sequelae**

Acquired brain injury (ABI) is an umbrella term for noncongenital brain injury encompassing both traumatic and nontraumatic etiologies. While the incidence and etiology varies by age, ABI is among the most common causes of morbidity and mortality in the world, led by insults associated with trauma, stroke, neoplasm, infection, and hypoxic-ischemic injury following cardiac arrest. Intracerebral hemorrhage (ICH) comprises a prominent ABI subgroup, accounting for 10 to 20 percent of all stroke-related ABI and affecting up to 50,000 people in the United States each year. Mortality rates can reach 55 percent, with half of the related deaths occurring in the first 48 hours. Hypertension is the most common risk factor, and hypertensive ICH classically occurs in the basal ganglia, thalamus, pons, and cerebellum. While MAOI-induced hypertension typically is reported in the context of co-consumption with tyramine-rich foods, caffeine itself is a weak MAO inhibitor, and its interaction with MAOIs has been implicated as a causative factor in severe hypertension.

For those who survive the acute insult, the sequelae of hypertensive ICH and ABI more broadly typically range from disorders of consciousness (DOC) in severe cases to varying blends of physical, cognitive, and psychosocial deficits often exacerbated by avoidable medical complications (e.g., pressure wounds and joint contractures). Generally, a trio of common cognitive deficits that include slowed processing speed, difficulty with multitasking, and reduced cognitive endurance build a foundation for the clinical challenges to come and help drive initial management. Patient-specific damage to individual brain areas and associated neural circuits adds layers of aggression, poor impulse control, impaired communication, and limited emotional awareness, all of which are further complicated by sleep disturbances, delirium, epilepsy, and a high incidence of depression. In terms of damage to individual brain areas, it is common for either the primary insult or subsequent secondary injury to involve the frontal and temporal lobes.

While there is more to the frontal lobe than motor function, motor deficits are particularly obvious and play an important role in postinjury functional independence. Posteriorly, the frontal lobe includes the primary motor (with its somatotopic organization, the “homunculus”) and premotor cortices.

**Figure 1: Relevant Neuroanatomy.** A. The frontal lobe (red) is responsible for executive function, motor planning, and motor output. The temporal lobe (blue) houses functions including special sensory processing, memory, and mood regulation. B. The basal ganglia (caudate, putamen, globus pallidus, subthalamic nucleus, substantia nigra) are comprised of multiple nuclei in the deep brain and are responsible for motor output and modulation. The thalamus is a cluster of nuclei and transmits responsible for sensory relay and arousal. Included in the medial temporal lobe are the hippocampus and the amygdala. The hippocampus is key in memory formation, and the amygdala contributes to memory consolidation and emotional response.
Projection fibers from the primary motor cortex dive downwards through the corona radiata and the posterior limb of the internal capsule to eventually form the corticobulbar and crossed corticospinal motor tracts. Both Broca’s speech area (associated with the classic aphasia) and the frontal eye fields (unilateral damage causing conjugate eye deviation to the side of the lesion) are located just anteriorly on the inferior and middle frontal gyri, respectively.

The prefrontal cortex, which begins anterior to the motor area is defined anatomically by its strong connection to the thalamus via projection fibers running through the anterior limb of the internal capsule. The prefrontal cortex is important clinically for its frequency of injury in traumatic brain injury and clinically challenging injury phenotypes. These syndromes can be characterized by emotional dysregulation and manic agitation, violence, social withdrawal with apathy, and perseveration.

Below the frontal lobe and within the lateral fissure itself, the insula is thought to play a broad role in social, emotional, and sensory processing (See Figure 1 on Page 2 and Table 1 at left).

Insular lesions from ABI are associated with a reduction in empathy, difficulty recognizing emotions (and associated facial expressions), and the subsequent development of central pain. Moving inferiorly, the temporal lobe folds medially to form major components of the limbic system, including the amygdala and, more posteriorly, the hippocampus. Damage to the amygdala specifically can result in a reduction in primary and social emotions, a diminished sense of danger, and aggressive, violent outbursts characteristic of intermittent explosive disorder. Insults to the hippocampus are commonly associated with memory deficits; specifically, hippocampal and parahippocampal damage is surmised to play a role in posttraumatic amnesia, and hippocampal variations are further hypothesized to contribute to the pathophysiology of psychosis.

<table>
<thead>
<tr>
<th>Table 1. Anticipated Impairments by Lesion Location</th>
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<tbody>
<tr>
<td><strong>Frontal Lobe</strong></td>
</tr>
<tr>
<td>Orbitofrontal</td>
</tr>
<tr>
<td>— Disinhibition</td>
</tr>
<tr>
<td>— Aggression</td>
</tr>
<tr>
<td>— Mania</td>
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<tr>
<td>— Disorganization</td>
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<tr>
<td>— Distractability</td>
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<tr>
<td>— Hypersexuality</td>
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<tr>
<td>— Hyperphagia</td>
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<tr>
<td>— Substance abuse</td>
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<tr>
<td>Dorsolateral</td>
</tr>
<tr>
<td>— Apathy</td>
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<tr>
<td>— Perseveration</td>
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<tr>
<td>— Pseudodepression</td>
</tr>
<tr>
<td>— Abulia</td>
</tr>
<tr>
<td>— Akinesia</td>
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<tr>
<td>— Impaired memory</td>
</tr>
<tr>
<td>— Decreased cognitive flexibility</td>
</tr>
<tr>
<td>Ventromedial</td>
</tr>
<tr>
<td>— Decreased emotional regulation</td>
</tr>
<tr>
<td>— Impulsivity</td>
</tr>
<tr>
<td>— Impaired social comprehension</td>
</tr>
<tr>
<td>— Decreased empathy</td>
</tr>
<tr>
<td><strong>Temporal Lobe</strong></td>
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<tr>
<td>Amygdala</td>
</tr>
<tr>
<td>— Anger</td>
</tr>
<tr>
<td>— Aggression</td>
</tr>
<tr>
<td>— Risk assessment</td>
</tr>
<tr>
<td>— Fear</td>
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<tr>
<td>— Anxiety</td>
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<tr>
<td>Hippocampus</td>
</tr>
<tr>
<td>— Memory</td>
</tr>
<tr>
<td>Wernicke’s Area</td>
</tr>
<tr>
<td>— Receptive communication</td>
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<tr>
<td>Insula</td>
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<tr>
<td>— Reduced empathy</td>
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<tr>
<td>— Poor facial expression recognition</td>
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<tr>
<td>— Difficulty recognizing emotions</td>
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<tr>
<td>— Central pain</td>
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</tbody>
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**Approach**

ABI clinical care is a multidisciplinary endeavor and begins by setting expectations via a shared understanding across the provider team, patient, and family. Practically, this means building rest breaks into patient schedules to manage limited cognitive endurance and minimize environmental stimulation and distractions. When it comes to disruptive behavior, staff and clinicians should be familiar with a standardized behavioral measure such as the Agitated Behavior Scale. This tool can supplement clinical assessment, inform management, and assess changes over time. Further, one-to-one supervision can offer a calming sense of security to the patient without chemical or physical restraint. The care team also should be aware that particularly problematic behavior may be amenable to a targeted plan that can help family and staff respond in a consistent, safe, and calming manner.
Affiliated with the University of Pittsburgh School of Medicine, UPMC Presbyterian Shadyside is ranked among America’s Best Hospitals by U.S. News & World Report.

While noncontrast head CT is performed acutely, MRI is more sensitive for depicting focal lesions, such as cortical contusion (MRI and CT are 98 percent and 56 percent sensitive, respectively) and traumatic axonal injury, which is rarely seen on CT.25,27 While research is ongoing regarding long-term prognostic utility, MRI findings are clinically associated with short-term dysfunction and can allow the care team to further anticipate near-term patient-specific challenges.25,28 Subsequently, neuroimaging can be correlated with the results of a neuropsychology evaluation to build a more functional understanding of patient-specific deficits in emotional, behavioral, and cognitive domains and to identify more subtle impairments that may otherwise be missed on clinical exam or in the therapy gym. To this end, the patient should be evaluated in different settings to capture a complete neurobehavioral picture, and findings should be discussed in-depth with the family and care team to smooth the transition into the rehabilitation setting, as well as prevent or minimize predictable behavioral complications.

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Consider</th>
<th>Avoid or Limit</th>
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| Hyper-Arousal, Agitation, Aggression | Propranolol  
Buspirone (delayed effects)  
Valproic Acid  
Lamotrigine  
Atypical Neuroleptics | Avoid typical antipsychotics  
Limit use of benzodiazepines |
| Poor Memory              | Donepezil                                      |                                                     |
| Sleep Disturbance        | Melatonin  
Trazodone  
Mirtazapine  
Prazosin  
Modafinil  
Zolpidem | Avoid benzodiazepines and GABA agonists |
| Depression               | Sertraline  
Escitalopram  
Citalopram  
Serotonin Norepinephrine  
Reuptake Inhibitors  
Trazodone  
Mirtazapine |                                                     |
| Apathy, Abulia  
4 | Methylphenidate  
Dextroamphetamine  
Amantadine  
Bromocriptine |                                                     |
| Psychosis                | Risperidone  
Olanzapine  
Other atypical neuroleptics | Avoid typical antipsychotics |

*Note that evidence supporting the use of the above medications is generally limited and that use is largely off-label. Further, the time-varying nature of recovery leads to evolving neuropharmacological effects, i.e., a medication that may be neuroprotective acutely after injury may become detrimental in the subacute to chronic phases of recovery and vice versa.

1 Anti-dopaminergic profile can exacerbate injury-associated hypodopaminergia and worsen cognitive and motor deficits.

2 May reduce anxiety as well.

3 Associated with impaired coordination, increased risk of falls, increased daytime sedation, negative effects on memory, slowed neurorecovery, and impaired neuroplasticity.

4 Potentially secondary to depression that should first be treated if appropriate.

Table 2. Select Pharmacotherapy in Sub-Acute ABI*25,30,31,32
Management

Redirection is the act of changing the focus of attention in order to stop undesirable behavior. In instances where patients perseverate on some offending stimulus, time should be taken to observe and identify what triggers may be present in the environment that can be removed or somehow modified. An increase in disruptive behavior during the day can often be associated with fatigue and reduced with structuring rest breaks into the schedule, along with ensuring adequate sleep at night. Relentless impulsivity coupled with diminished safety awareness makes constant, one-to-one observation impractical even for the most robustly staffed units, so the use of restraints such as seatbelts and canopy beds should be considered.

However, nonpharmacological interventions can be inappropriate in the case of severe aggression, and pharmacotherapy is often required to manage behaviors that jeopardize safety or undermine the rehabilitation process (See Table 2 on Page 4).

Before introducing new agents, reducing polypharmacy is the first step. Target medications include most anticonvulsants, antipsychotics with antidopaminergic characteristics (especially haloperidol and chlorpromazine), benzodiazepines, anticholinergics, and opiates. Many psychoactive agents can be quite sedating at relatively low doses in the ABI population and are often used in acute care. While potentially appropriate in that setting, over-sedation should not be confused for good control of problematic behaviors and should be reversed quickly in the rehabilitation setting.

Atypical neuroleptics such as risperidone and quetiapine are commonly used acutely for their sedating properties and enjoy a favorable side effect profile. Other atypicals, such as olanzapine and ziprasidone, have the added flexibility of intramuscularly injectable formulations. With chronic aggression, beta-blockers, and specifically propranolol, have the best track record for efficacy. Antiepileptics such as carbamazepine and valproic acid also can be useful, in particular for patients being managed for seizures on other agents. Aggression and agitation driven or accompanied by anxiety can be particularly responsive to buspirone or SSRIs, such as fluoxetine and sertraline.

Sleep should diligently be logged and proactively managed if insufficient. We recommend starting with melatonin for sleep problems due to its minimal risk of side effects. Although evidence is poor, there is considerable use in the field of trazodone at low doses. Zolpidem can be used, but caution should be exercised in that rare instances of paradoxical activation have been documented in the literature and observed by our team. An alternative approach with modafinil, an agent that increases wakefulness, can be employed to keep the patient more active during the day and potentially increase the likelihood of sleeping at night.

Depressed mood is a common problem in brain-injured patients. Of the available treatments, SSRIs have the most favorable side-effect profile and are considered first-line, with sertraline, escitalopram, and citalopram preferred for their shorter half-lives, minimal anticholinergic activity, and decreased interaction with other medications. The serotonin-norepinephrine reuptake inhibitors also have good potential in the treatment of depression, and among them, venlafaxine has the added potential benefit of activation. Trazodone and mirtazapine are novel antidepressants with favorable side-effect profiles to help with sleep.

While apathy can accompany depression, it also can present independently in the ABI population and should be treated as a separate entity. Stimulants and pro-dopaminergic medications such as amantadine, bromocriptine, and methylphenidate are useful in treating apathy.

Psychosis should be treated when it causes distress to the patient or drives problematic behaviors that interfere with therapy participation or safety. Atypical neuroleptics are preferred due to their favorable side-effect profile, and there are published case reports using risperidone, clozapine, and olanzapine, but more substantive data are lacking. In the absence of strong recommendations, the most prudent path to follow is the adage “start low and go slow” while trying different agents after adequate trials to find the optimal benefit for each patient.

In patients who cannot clearly communicate pain symptoms, scheduling analgesic medications such as acetaminophen and nonsteroidal anti-inflammatories (NSAIDs) is an important pre-emptive strategy. Topical lidocaine in gel or patch form can be helpful for focal pain. Gabapentin, tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) are beneficial for neuropathic pain, but providers should monitor for sedation and cognitive impairment. Opioids should be used with caution due to the risk for sedation in this more sensitive patient population.

Agitation, aggression, anxiety, irritability, and the other neurocognitive features of ABI can be quite distressing to loved ones without context, so family education should be given as
Family invariably know their loved ones better than clinical staff and may have valuable insight into both interpreting behaviors and identifying motivating factors to shape them. The family also will be responsible for caring for the patient if discharged home and should be involved in developing the care plan. To this end, the most critical component of family education is determining goals for their loved one’s rehabilitation and compassionately grounding their expectations of recovery in reality.

**Clinical Vignette Outcome**

The day after admission to the ABI rehabilitation unit, the team met with the patient’s wife to discuss his condition and plan of care. She articulated significant concerns about the team’s focus on her husband’s behavioral presentation at the expense of his physical impairments. She argued that he “was not crazy” and did not want him treated as such. She was educated at length on the neurobehavioral sequelae of ABI, specifically concerning the areas of her husband’s brain that were affected. The imaging was reviewed with her in detail, and attention was called to hemorrhagic extension into the right frontal and medial temporal lobes (See Images 2 and 3). This proved quite beneficial to building trust with the patient’s family, and going forward, there was more receptiveness to suggested medication interventions.

The patient and his wife agreed to a headache cocktail, including valproic acid on day 3. Over the next week, this medication was titrated and augmented with propranolol to excellent effect, evidenced by a significant improvement in therapy participation, resolution of physical aggression and agitated outbursts, and somewhat diminished anxiety. MH agreed to wear his helmet and began taking meals in the dining room among the other patients. He did continue to experience visual and auditory hallucinations and often perseverated on the delusion that his wife was constantly present at his side. He also endorsed depressed mood and perseverated on needing an antidepressant out of the fear of becoming more depressed and potentially suicidal. To treat these disabling symptoms, the patient was started on aripiprazole on day 16 with further significant improvements.

MH required no further medication adjustments from this point and demonstrated considerable motor recovery in the following weeks. He was briefly discharged to neurosurgery for cranioplasty, after which he returned for two more weeks until discharge home, 70 days following his hemorrhage. On discharge, he was able to walk 250 feet with a left ankle foot orthosis, a straight cane, and the assistance of his wife. He has transitioned from his cocktail of psychoactive medications to escitalopram monotherapy with no regression. He is now walking only needing his ankle brace.

**Image 2:** Axial T2 FLAIR sequence of the patient several weeks into his acute inpatient rehabilitation course demonstrating resolving blood products but still significant edema of the right basal ganglia and descending white matter tracts.

**Image 3:** Axial T2 FLAIR sequence of the patient several weeks into his acute inpatient rehabilitation course demonstrating significant edema of the right temporal lobe white matter, also affecting the medial structures, including the amygdala and hippocampus.
References

ABOUT THE DEPARTMENT OF PHYSICAL MEDICINE AND REHABILITATION

- UPMC Presbyterian Shadyside is ranked by U.S. News & World Report as one of the nation’s best hospitals for rehabilitation.

- The Department of Physical Medicine and Rehabilitation is consistently a top recipient of NIH funding for rehabilitation-related research.

- The Spinal Cord Injury Program at UPMC is one of only 14 in the country selected by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) as a model for other rehab providers.

- Department clinicians lead UPMC’s rehabilitation network of more than 90 inpatient, outpatient, and long-term care facilities — one of the country’s largest.