Refining Delirium: A Transtheoretical Model of Delirium Disorder with Preliminary Neurophysiologic Subtypes

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The development of delirium indicates neurophysiologic disruption and predicts unfavorable outcomes. This relationship between delirium and its outcomes has inspired a generation of studies aimed at identifying, predicting, and preventing both delirium and its associated sequelae. Despite this, evidence on delirium prevention and management remains limited. No medication is approved for the prevention or treatment of delirium or for its associated psychiatric symptoms. This unmet need for effective delirium treatment calls for a refined approach. First, we explain why a one-size-fits-all approach based on a unitary biological model of delirium has contributed to variance in delirium studies and prevents further advance in the field. Next, in parallel with the shift from dementia to "major neurocognitive disorder," we propose a transtheoretical model of "delirium disorder" composed of interactive elements—precipitant, neurophysiology, delirium phenotype, and associated psychiatric symptoms. We explore how these relate both to the biopsychosocial factors that promote healthy cognition ("procognitive factors") and to consequent neuropathologic sequelae. Finally, we outline a preliminary delirium typology of specific neurophysiologic disturbances. Our model of delirium disorder offers several avenues for novel insights and clinical advance: it univocally differentiates delirium disorder from the phenotype of delirium, highlights delirium neurophysiology as a treatment target, separates the core features of delirium from associated psychiatric symptoms, suggests how procognitive factors influence the core elements of delirium disorder, and makes intuitive predictions about how delirium disorder leads to neuropathologic sequelae and cognitive impairment. Ultimately, this model opens several avenues for modern neuroscience to unravel this disease of antiquity. (Am J Geriatr Psychiatry 2018; ■■:■■–■■)

Key Words: Delirium model, neurophysiology, subtypes, encephalopathy, neurocognitive disorder, cognitive decline

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Highlights

- The immense clinical and neurophysiologic diversity in delirium suggests that the current one-size-fits-all approach may be misguided.
- We propose a refined model of delirium disorder composed of interactive elements that elucidates key relationships and clarifies delirium nomenclature.
- Our transtheoretical model highlights delirium neurophysiology as a novel treatment target.
- We introduce a preliminary list of delirium disorder subtypes based on underlying neurophysiologic disturbance(s).

INTRODUCTION

The development of delirium alerts clinicians to neurophysiologic compromise and often foreshadows long-term cognitive and functional decline.[1,2] That delirium is associated with poor outcomes has been known for decades,[3] and this knowledge has generated fervent interest in identifying delirium predictors with the goal of enhancing risk stratification[4] and ultimately preventing delirium.[5] However, as important as prevention is, current delirium prevention protocols fail to prevent delirium in over 60% of cases.[6,7] Furthermore, there is no consensus on the best strategy to manage delirium after onset, and there is no conclusive evidence that by ameliorating the symptoms of delirium we prevent the poor physical and cognitive outcomes currently attributed to it.

Despite definitive advances in recognition and understanding of its sequelae, little progress has been made in understanding the neurophysiology of delirium beyond Lipowski's authoritative work over a quarter century ago.[8,9] Current delirium management protocols advocate for proactive screening, with the assumption that case finding improves care and leads to effective treatment.[10] Once delirium occurs, though, interventions may have limited effect on managing its symptoms or hastening its resolution.[11,12] Further, whereas delirium commonly resolves in a few days as its underlying cause improves,[13] it may persist for weeks even after the initial precipitants have resolved.[14,15] Currently, no medication is approved by the U.S. Food and Drug Administration to prevent or treat delirium, and nonpharmacologic interventions have failed to demonstrate clear efficacy in managing delirium.[11]

The lack of concrete delirium treatment options represents an urgent, unmet need,[16] and we believe this reflects our limited knowledge of the condition.[17] Thus, we need to refine our understanding of delirium in order to enhance the clinical utility of diagnosis, elucidate how delirium associates with poor outcomes, and advance our understanding of its neurophysiology.[17–19] We have three aims: 1) to explain our rationale for refining delirium; 2) to introduce a transtheoretical model of delirium disorder that divides it into its component parts, thereby offering novel clinical and research inroads; and 3) to propose a delirium typology based on discrete neurophysiologic disturbances. In so doing, we hope to inspire a disruptive shift in the field of delirium that holds promise for clinical advance.

Why We Need to Refine Delirium

Our goal is to create a more accurate and precise model of delirium with clear research and treatment implications. In the traditions of Engel and Romano[20] and Lipowski,[8] delirium is commonly, though not unanimously,[21] viewed as a unitary condition that represents a shared "final common pathway."[22] A convergent phenotype, though, does not imply that all deliria are created equal.[23] For instance, not all cases of heart failure have the same etiology.[24] Although many heart failure patients express similar physical findings (i.e., phenotype), heart failure itself is caused by discrete pathophysiologic entities (e.g., ischemia, autoimmunity). Further, these specific causes require disease-specific management with some commonalities in the management of the convergent phenotype (e.g., diuresis for fluid overload). Similarly, we suggest that subsumed under the clinical entity of delirium are discrete neurophysiologic conditions that cause convergent clinical features.

Box 1. Clinical Factors that Contribute to Substantial Variance in Delirium Studies

- Delirium phenotypes are heterogeneous and may fluctuate widely, both within patients and in a relatively short period. This variability challenges our understanding of the neural circuits involved in each case.
- Although a telltale sign of underlying neurophysiologic disruption, delirium is an insensitive clinical sign. Therefore, it cannot be used as a reliable screening tool for medical illness (i.e., not every patient exposed to diphenhydramine[25] or experiencing sepsis[26] develops delirium).
- Delirium is nonspecific for cause. Like fever, delirium may be due equally to anticholinergic toxidrome or sepsis. Similarly, both alcohol intoxication and withdrawal can present with delirium.
- The development of delirium is not necessary for the development of long-term cognitive impairment after acute medical illness. Even subsyndromal delirium may be associated with significant neuropathologic insults.[27]
- The development of delirium alone is insufficient to cause negative long-term sequelae.[1]

Several additional factors conspire against developing a one-size-fits-all approach to delirium (Box 1). In particular, investigations into delirium biomarkers have yielded inconsistent findings,[28,29] and studies of neuroleptics for delirium prevention and treatment have produced heterogeneous results.[30] These findings may suggest a plurality of neurophysiologically distinct conditions under our current umbrella term. Attempts to collate these validating factors[31] into a unitary biological model called delirium may be holding us back from refining our understanding and approach to this multiplex syndrome.

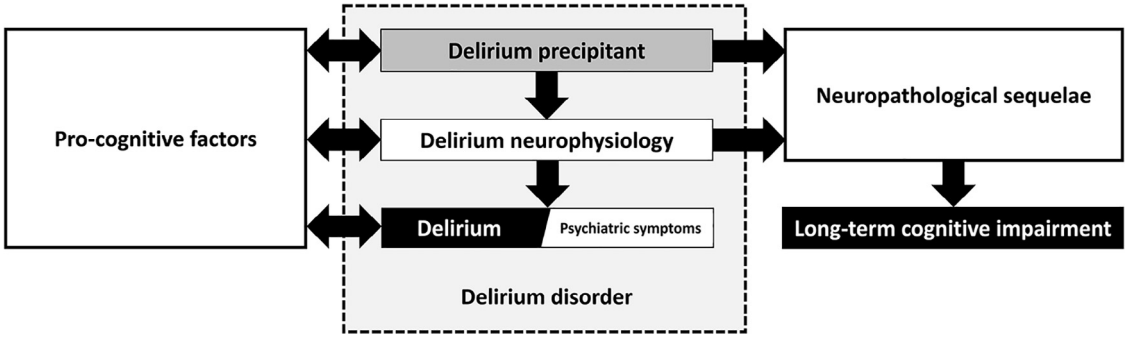
Although a patient with delirium is at risk of permanent, irreversible brain damage, the nature of this predictive association remains poorly understood. Similar to how outcomes after surgery are susceptible to confounding by indication,[32,33] delirium outcome studies are susceptible to confounding by comorbidity, illness severity, and underlying neurophysiologic resilience or its converse vulnerability (sometimes called allostasis).[34,35] We predict that the relationship between delirium and many of its associated poor outcomes may prove epiphenomenal.[36] This is because current models of comorbidity, such as the Charlson Comorbidity Index, are incomplete, our measures of illness severity are similarly limited, and we have no reliable way to assess neurophysiologic resilience or vulnerability.

Delirium Disorder: The Model

We propose a transtheoretical model of delirium disorder (Figure 1) that divides the condition into its interactive elements. Current delirium nomenclature is problematic because "delirium" indiscriminately describes both the clinical syndrome and a diagnosable disorder, which makes clear discussion about the condition difficult. Hereafter, we will restrict the term delirium to the clinical phenotype, and we introduce the term *delirium disorder* for the diagnosable condition as an analog to other Diagnostic and Statistical Manual (DSM) diagnoses (e.g., dementia has been relabeled major neurocognitive disorder).

This model illustrates that delirium disorder (i.e., shaded, dashed box at Figure 1 center) occurs when one or more delirium precipitants lead to neurophysiologic disruption, in turn causing delirium (again, the clinical phenotype). Patients with delirium disorder typically, but not always, exhibit additional associated psychiatric symptoms that extend beyond the core features of delirium. Delirium and its associated psychiatric symptoms are shaded differently in Figure 1 to emphasize this distinction and encourage clinical differentiation between these associated psychiatric symptoms and the core features of the delirium phenotype. The arrows in Figure 1 represent causal contingencies. That is, although there are circumstances under which each may occur, causal pathways are not implied. For instance, a neurophysiologic disturbance that may cause delirium in certain circumstances may lead to subsyndromal delirium in others. As this model implies, identifying discrete neurophysiologic processes would invite novel opportunities for managing delirium and for preventing long-term cognitive impairment due to neuropathologic sequelae. Below we define the interactive elements of our model.

FIGURE 1. Trans-theoretical model of delirium disorder. This model divides delirium disorder into its interactive elements to reveal key relationships.



Delirium Disorder. DSM-5 and International Classification of Diseases, Tenth Revision, delirium diagnoses each require the presence of delirium and at least one precipitant presumed to lead to a neurophysiologic disturbance that mediates the relationship between precipitant and phenotype. Delirium disorder, then, encompasses precipitant, neurophysiologic disturbance, and delirium. This proposal is further intended to parallel the recent transition in DSM-5 from dementia to major neurocognitive disorder.

Delirium. We use this specifically to describe the core clinical features that define delirium—that is, the delirium phenotype. Though delirium typically implies neurophysiologic compromise and a biological precipitant, it is agnostic to these. It includes a change in cognition, impaired awareness, inattention, disorganized thinking, and fluctuations in arousal. Delirium has a severity[37] and duration,[1] each of which is associated with outcomes. Curiously absent from the definition of delirium is its functional impact. Delirium nearly universally causes functional impairment (e.g., inattention that impedes rehabilitation efforts), much the same way that the convergent clinical features of heart failure (e.g., exertion intolerance and edema) do.

Psychiatric Symptoms. Although clinicians may use the word delirium casually to refer to the psychiatric symptoms occurring with delirium (e.g., speaking of a patient as "floridly delirious" or having an "agitated delirium"), the core features of delirium should be differentiated from its associated psychiatric symptoms. Notably, most interventions, such as neuroleptics, used to "treat delirium" are aimed principally at these symptoms. These may include both positive symptoms (i.e., aggression, impulsivity, affective dysregulation, social disinhibition, perceptual disturbances, and delusions) and negative symptoms (i.e., avolition, withdrawal, and anhedonia).

Delirium Precipitants. These entail the biological insults or "causes" that lead to delirium by way of neurophysiologic disruption. They may include medical and surgical conditions as well as psychoactive substances. Often, more than one delirium precipitant will be identified.[38]

Delirium Neurophysiology. Neurophysiologic disruption in delirium is complex, but emerging data suggest that there are discrete neurophysiologic routes from a given delirium precipitant to the convergent phenotype of delirium. As we explore in section 3 below, a model of delirium disorder that includes discrete neurophysiologic subtypes stands to elucidate key relationships between neurophysiology and both its upstream precipitants and its resultant phenotype.

Procognitive Factors. These baseline biopsychosocial factors are integral to promoting healthy cognitive function (Table 1) and explain how each person is variably resilient or vulnerable to delirium. Disruption in procognitive factors 1) may modify the neurophysiologic impact of delirium precipitants; 2) may influence neurophysiologic disturbances, thereby potentiating, propagating, or mitigating delirium; or 3) if severe enough may serve as an independent delirium precipitant. Defining

TABLE 1. Procognitive Factors

Procognitive factor	Relationship with cognition	How disruption may compromise cognition
Baseline neural integrity	Key neural networks are involved in generating consciousness and cognition,[39] and the correlation between neural integrity and mental capacity is exemplified in clinicopathologic studies. Developmental and acquired neurocognitive disorders predispose to delirium.[40] The most common application is in older adults—especially those with cognitive impairment at baseline—who have accrued neural insults ("neuronal aging hypothesis").[22]	Insults to neural integrity may lead to reduced resilience in response to acute neurophysiologic stress,[41] with certain networks such as the default mode network playing more important roles.[42]
Resting brain perfusion	Chronic hypoperfusion, as in cerebrovascular disease or heart failure, represents vulnerability to delirium. Acute hypoperfusion (or isolated hypoxia) compromises brain function and leads to delirium.[43] Chronic hypoperfusion has also been implicated in not only vascular cognitive impairment[44] but Alzheimer[45] dementia.	Metabolic disruption and energy deficiency leading to oxidative stress and neurotransmitter dysfunction.
Nutritional status	Adequate nutrition is required for all levels of health. Acute deficiency in several B vitamins (B1, B3, B6) may cause delirium,[46] and both folate and B12 deficiencies are associated with cognitive decline. Studies of specific diets and dietary health find an association between undernutrition and cognitive decline.[47] Interestingly, several nutrients are involved in DNA methylation and other epigenetic changes.[48]	Metabolic disruption and energy deficiency may lead to oxidative stress and neurotransmitter dysfunction.
Hydration status	Dehydration itself is a common cause of hospital admission among older adults.[49] Loss of as little as 1%–2% of body water can impair cognition.[50]	Metabolic disruption may lead to oxidative stress and neurotransmitter dysfunction.
Sleep and circadian rhythm integrity	Sleep deprivation or restriction influences arousal, attention, memory, and state stability.[51,52] Interventions to restore circadian rhythms have shown promise in preventing delirium.[53] Circadian rhythms extend to all organ systems, including, for instance, general metabolism,[54] immune function,[55] and endocrine system.[56]	Dyssynchrony among brain regions along with multi-system organ dysfunction (cardiovascular, immune, endocrine, et al.).
Adequate sensory stimulation	The neuropsychological effects of sensory deprivation have been studied for more than half a century.[57] In a classic report, delirium was attributed to bilateral eye patching.[58] Sensory overload, on the other hand, remains poorly understood.[59] Current nonpharmacologic approaches to delirium emphasize adequate sensory stimulation, though the independent effect sensory deprivation or overload has on causing or potentiating delirium remains unclear.	Unclear. Sensory deprivation may lead to release phenomena akin to Charles Bonnet syndrome. Perhaps nociceptive stimuli contribute to sensory overload.
Physical activity level	Early physical and occupational therapy of mechanically ventilated ICU patients reduces delirium duration and increases ventilator-free days.[60] In general, physical activity and exercise play a critical role in maintaining cognitive health[61] and are of particular interest in older people.[62] Conversely, advancing frailty, which commonly includes measures of physical activity, vigor, and speed, confers vulnerability to delirium.	Unclear. Daytime inactivity may blunt circadian rhythms, lead to muscle and bone deterioration, and contribute to poor engagement in care and recovery.
Cognitive activation	Cognitive stimulation therapy, a type of group therapy, enhances functioning and quality of life in patients with cognitive impairment.[63] Nevertheless, it remains to be proven if cognitive training enhances fluid intelligence in healthy adults[64] or whether mental exercise prevents cognitive decline.[65]	Unclear. Conscious activity turns off the default mode network and activates task-positive networks. Investigations on network activity and connectivity may offer insights into the value of cognitive activation.
Degree of socialization	Socialization requires higher order executive function and interpersonal acumen that is often more than the sum of its parts. Socialization is critical for overall well-being and quality of life, though evidence of its effects on cognition remains preliminary.[66]	Unclear. As with cognitive activation above, socialization requires activation and coordination of complex neural networks.

procognitive factors as such provides a biological rationale for the benefits of multicomponent, nonpharmacologic interventions in preventing and managing delirium.

Neuropathologic Sequelae. A delirium precipitant or the neurophysiologic disruption it causes may lead to persisting neuropathologic changes—either neuronal or extraneuronal—leading to the development

of long-term cognitive and functional impairment.[67] Neuronal pathology may include necrosis, apoptosis, atrophy, edema, axonal injury, or cytoarchitectural change (i.e., intraneuronal deposition, inclusion bodies, or mineralization). Extraneuronal pathology may involve gliosis, microglial activation, or demyelination.

By characterizing our model as transtheoretical, we mean to differentiate it from previous theory-specific models (e.g., the cholinergic deficiency hypothesis) because it provides a heuristic framework of interactive elements rather than advocates for the primacy of one unifying neurophysiologic model.[22] It draws upon previous hypotheses and, as detailed below, attempts to make their valuable insights actionable. Certain upstream neurophysiologic disturbances (e.g., electrolyte disturbances) will lie closer to the proximal delirium precipitant, whereas downstream effects (e.g., network dysconnectivity) may begin to merge as they near common final pathway(s).[68] It is possible that the best substantiated models to date have the most robust evidence because these findings (again, e.g., cholinergic deficiency) are found in the most common types of delirium disorder (e.g., among medically ill older adults) but may not apply to other types (e.g., alcohol withdrawal delirium in middle age). We emphasize that this transtheoretical model is enhanced by ongoing attempts to develop further candidate models of delirium neurophysiology.[41]

It is not well understood how procognitive factors or their deficiency share a relationship with each of the elements of delirium disorder depicted in our model, despite clear evidence in the literature that such relationships exist.[69,70] We posit that each of these relationships is likely bidirectional. Deficits in procognitive factors (e.g., poor nutrition) can rise to the level of a delirium precipitant (e.g., thiamine deficiency); conversely, delirium precipitants (e.g., surgery) can negatively affect procognitive factors (e.g., via postoperative physical inactivity). Next, deficits in procognitive factors (e.g., resting brain hypoperfusion) can generate delirium neurophysiology (i.e., oxidative stress and perhaps epigenetic changes[48]); conversely, delirium neurophysiology (e.g., neuroinflammation) can disrupt procognitive factors (e.g., sleep and circadian rhythms). Finally, a deficiency in certain procognitive factors (e.g., social withdrawal) may cause features of delirium (e.g., hypoactivity), whereas hypoactive delirium may compromise other procognitive factors (e.g., nutrition and hydration). The relationship between procognitive factors and delirium disorder is especially relevant for those with dementia because such patients have high baseline vulnerability to delirium precipitants[71] and may be uniquely vulnerable to neurophysiologic insults[70] and exhibit uniquely discordant clinical features when evaluated using a phenomenology-based approach.[72]

The severity and duration of delirium are associated with neuropathologic sequelae and development of long-term cognitive impairment.[1,37] However, it is not yet clear which precipitants are more offensive than others, which neurophysiologic abnormalities are more likely to cause these negative outcomes, or how they do so.[70] It stands to reason that different precipitants, along with their attendant neurophysiologic disturbances, will lead to different neuropathologic sequelae. Thus, this model offers some guidance for targeted research in these areas.

Whereas all aspects of delirium are clinically meaningful, their meaning varies with clinical situation. Consider the three clinical examples in Table 2. As illustrated in the second of these examples, the core features of delirium and its associated psychiatric symptoms are not benign; they can cause personal distress, compromise recovery from illness, disrupt care, and lead to mechanical or other medical interventions that subsequently cause adverse outcomes. However, these effects should be differentiated from the neuropathologic sequelae due to specific delirium precipitants and/or delirium neurophysiology. We underscore that any relationship between neuropathologic sequelae and either delirium precipitant or neurophysiology is causally contingent: not all precipitants or neurophysiologic states that cause delirium cause neuropathology. We should be careful not to implicate delirium, the syndrome, as directly neuropathogenic. That is, any relationship between delirium and adverse outcomes should have a biologically plausible explanation.[75]

Studies of how delirium is associated with negative outcomes are beginning to emerge,[70,74] but it remains unclear which neurophysiologic types of delirium disorder contribute to these untoward outcomes. Provocatively, recent findings in a murine model of delirium suggest that the physiologic precipitant for certain types of delirium may even be mechanistically dissociable from the physiologic causes

TABLE 2. How Delirium and Its Psychiatric Symptoms May Be Associated With Outcome

	Case 1	Case 2	Case 3
Clinical scenario	Midazolam use for procedural sedation in an adult. No postprocedural cognitive impairment occurs.	A patient who develops delirium with psychiatric symptoms and injures himself due to agitation.	A critically ill patient with delirium due to sepsis who develops irreversible cognitive impairment (i.e., fails to return to premorbid cognitive baseline).
Description of relationship	Delirium is due to a nonpathogenic, reversible neurophysiologic change.[32] Here, no lasting cognitive impairment occurs.	Delirium may present with behavioral or psychological symptoms such as agitation or persecutory delusions. Here, the negative outcome is mediated by a behavioral disturbance.	Delirium reflects an underlying pathogenic brain state, which in turn causes cognitive decline and accelerates brain aging.[73] Here, cognitive decline is due to a pathogenic brain insult, not delirium itself.
Clinical relevance	Not all delirium may presage negative outcomes. Delirium indicates a neurophysiologic disturbance, and defining the disturbance and any upstream precipitants is key. Delirium may also alert to reduced cognitive resilience.	Psychiatric symptoms of delirium may cause injury and lead to interventions (e.g., restraints) that then compromise outcomes.[74] Persistent inanition may lead to deconditioning, pressure ulcers, contractures, et al.	Delirium *may* herald an underlying neuropathologic process which leads to long-term cognitive impairment. The relationship between delirium and outcome, again, is epiphenomenal.

of brain injury manifesting as irreversible cognitive impairment.[76] A transtheoretical model of delirium disorder that identifies interactive relationships, as described above, offers a mechanistic approach to identifying targets for basic science research and informs clinical trials aimed at improving outcomes.

Subtyping Delirium Disorder by Neurophysiology

The limitations of the current delirium subtypes have been debated for decades.[9,24] Psychomotor activity is the most common means of delirium subtyping; however, motoric subtypes may be unstable over time,[77] and though they can provide clues to neurophysiology (i.e., increased activity of gamma-aminobutyric acid in hepatic encephalopathy may contribute to delirium), they principally acknowledge arousal level. Geographic delirium (e.g., postoperative delirium, ICU delirium, delirium superimposed on dementia) is another common method of delirium subtyping. Invoking clinical context is pragmatic because it aggregates shared vulnerabilities, risk factors, clinical features, and similar clinical interventions along with their attendant physiologic effects. Such approaches do limit some variance across deliria, but this is liable to create a mirage of biological coherence.

Just as the field of neurocognitive disorders has emphasized the need to specify etiology (DSM-5 lists 13 etiologic subtypes of major neurocognitive disorder),[78] the delirium field ought to consider adopting a similar approach. The five current DSM-5 delirium subtypes (i.e., substance intoxication delirium, substance withdrawal delirium, medication-induced delirium, delirium due to another medical condition, and delirium due to multiple etiologies) are inadequate for this purpose. In Table 3 we provide common types of delirium disorder based on precipitants, describe associated neurophysiology, and outline precipitant-specific interventions.

Based on review of common delirium precipitants in Table 3, we outline a preliminary typology of delirium neurophysiology in Table 4, which builds on previous efforts to organize the complex underpinnings of delirium.[21,90] Our goal is to make recent work on models of delirium actionable to improve clinical care. For each neurophysiologic type, an illustrative prototype is suggested along with theorized avenues for translational interventions based on discrete neurophysiology. We should not expect one type of neurophysiology-guided intervention to be effective for all types of delirium disorder despite indistinguishable phenotypes (e.g., dexmedetomidine may effectively combat postoperative noradrenergic overactivity but would be unlikely to address cumulative effects of brain aging).

A case of delirium disorder with multiple precipitants may exhibit features of more than one kind of delirium neurophysiology. Consider, for instance, a patient with urinary tract infection and hyponatremia

TABLE 3. Common Delirium Precipitants With Associated Neurophysiology and Current Interventions

Delirium precipitant	Candidate neurophysiology	Precipitant-specific interventions
Peripheral infection (e.g., urinary tract infection)[79]	Neuroinflammation	Antibiotics
Sepsis-associated encephalopathy	Oxidative stress Neuroinflammation Neuropathologic sequelae include microvascular ischemia and hemorrhage	Antibiotics and circulatory support
Cerebral hypoperfusion (heart attack or heart failure) or hypoxia (COPD or pulmonary embolism)	Oxidative stress	Restore circulation to hypoperfused, ischemic, or hypoxic tissues
Electrolyte disturbances (e.g., hyponatremic encephalopathy)	Neurotransmitter dysfunction	Careful correction of disturbances
Postoperative state[a]	Neuroinflammation	Nonpharmacologic interventions alone
Paraictal encephalopathy	Network dysconnectivity	Antiepileptics for seizures, though their use for encephalopathy per se is untested
Traumatic brain injury[80]	Glutamatergic overactivity Oxidative stress Associated structural damage (DAI, focal ischemia, BBB breakdown)	Nonpharmacologic interventions[81]: amantadine has been studied later in recovery,[82] and neuroleptics in particular may hinder cognitive recovery[81]
Uremic encephalopathy[83]	Neuroinflammation Oxidative stress Glutamatergic overactivity (due to uremic toxins, especially nitric oxidase-inhibiting guanidine compounds)	Renal replacement
Cystocerebral syndrome (i.e., encephalopathy due to urinary retention)[84]	Dysautonomia (afferent β_3-adrenergic activation due to bladder distention)	Bladder decompression
Hepatic encephalopathy	Glutamatergic overactivity (due to high ammonia)[85] Cerebral edema related to elevated glutamine Neuroinflammation	Lactulose ± rifaximin *Early evidence*: probiotics, branched-chain amino acids, L-ornithine L-aspartate, flumazenil (benzodiazepine antagonist)
Valproic acid (VPA)-associated hyperammonemic encephalopathy	Glutamatergic overactivity[86] (VPA-induced carnitine deficiency → high ammonia → glutamate excess) Cerebral edema related to elevated glutamine[87,88]	Levocarnitine and discontinue valproic acid
Anticholinergic toxidrome	Cholinergic deficiency	Physostigmine (optional/potentially diagnostic)
Corticosteroid intoxication	Neuroendocrine (HPA axis)	Limit corticosteroids as feasible
Benzodiazepine intoxication	GABA-ergic overactivity	Flumazenil (optional/potentially diagnostic)
Alcohol withdrawal delirium	Glutamatergic overactivity Dysautonomia (excess noradrenergic tone)	Benzodiazepine *Early evidence*: valproic acid, carbamazepine
Malignant catatonia	GABA-ergic deficit Glutamatergic overactivity Dysautonomia (excess noradrenergic tone)	Benzodiazepines and electroconvulsive therapy *Early evidence*: NMDA receptor antagonists, valproic acid, carbamazepine, thyroid (T3) supplementation
Anti-NMDA receptor encephalitis	Glutamatergic overactivity Neuroinflammation	1st line: corticosteroids ± IVIG/plasmapheresis 2nd line: rituximab, cyclophosphamide, and less commonly the antimetabolites azathioprine, mycophenolate, methotrexate

Notes: BBB: blood-brain barrier; COPD: chronic obstructive pulmonary disease; DAI: diffuse axonal injury; GABA: gamma-aminobutyric acid; HPA: hypothalamic-pituitary-adrenal; IVIG: intravenous immunoglobulin; VPA: valproic acid.

[a]Neurophysiology may differ based on surgery and type of anesthesia. Use of cardiopulmonary bypass may also influence outcomes and, as such, research in postoperative delirium not uncommonly divides major operations into cardiac and noncardiac surgery.

who is on several anticholinergic medications. Similarly, even in certain delirium disorders with a common precipitant, a patient may have multiple concurrent neurophysiologic types present (see hepatic encephalopathy and sepsis-associated encephalopathy in Table 3). Therefore, where multiple types of delirium neurophysiology are present, patients may benefit from multipharmacologic interventions that target each physiologic disturbance—analogous to using multicomponent nonpharmacologic interventions to target several procognitive factor deficiencies simultaneously. Of course, such an approach would

TABLE 4. Delirium Disorder Subtypes Based on Neurophysiology

Delirium neurophysiology	Prototype	Theorized translational intervention
Neuroinflammation[a]	Postoperative delirium Pneumonia-associated delirium Paraneoplastic encephalitis	Anti-inflammatory interventions (e.g., minocycline, NSAIDs), therapeutic hypothermia, intravenous immunoglobulin
Oxidative stress	Cardiac arrest	Antioxidant compounds (e.g., N-acetyl cysteine, high-dose vitamins), therapeutic hypothermia, supraphysiologic melatonin
Cerebral edema[89]		
• Vasogenic	Mechanical brain injury	Glucocorticoids, aquaporin 4 inhibitor (e.g., piroxicam), VEGF inhibitors
• Cytotoxic	Hyponatremic encephalopathy	Sulfonylurea inhibitors (e.g., glibenclamide), NKCCl inhibitors (e.g., bumetanide)
• Increased intracranial pressure	Acute hydrocephalus	Mannitol, hyperventilation
Neuroendocrine (HPA axis)	Corticosteroid psychosis	Antiglucocorticoids (e.g., ketoconazole or mifepristone)
Circadian arrhythmia	Sleep restriction/deprivation as in hyperthyroidism or perhaps mania	Light therapy, melatonin agonist therapy, use of nondeliriogenic hypnotics, regulating circadian rhythm of sleep-wake cycle, physical activity, feeding, et al.
Brain aging	Sundowning ("nocturnal delirium")	Emphasize nonpharmacologic interventions, limit/avoid psychoactive medications
Neurotransmitter dysfunction[b]		
• Cholinergic deficiency	Anticholinergic toxidrome	Cholinesterase inhibitors (e.g., physostigmine)
• Glutamatergic overactivity	Anti-NMDA receptor encephalitis	NMDA receptor antagonist, gabapentin/pregabalin, calcium channel modulators (lamotrigine, VPA)
• GABA-ergic overactivity	Benzodiazepine intoxication	Benzodiazepine receptor modulators
• Dopaminergic overactivity	L-DOPA intoxication	Dopamine receptor modulators
• Serotoninergic overactivity	Serotonin syndrome	Cyproheptadine or mirtazapine
• Noradrenergic overactivity	Alcohol withdrawal delirium	α1-antagonist, α2-agonist, β-blocker
Network dysconnectivity	Multifactorial delirium	Postoperative early ambulation or other nonpharmacologic interventions incorporating procognitive factors, which may have multisystem benefits

Notes: GABA: gamma-aminobutyric acid; HPA: hypothalamic-pituitary-adrenal; NMDA: N-methyl-D-aspartate; NSAIDs: nonsteroidal anti-inflammatory drugs; VEGF: vascular endothelial growth factor; VPA: valproic acid.

[a]Neuroinflammation likely involves several overlapping subtypes, including cytokine-predominant responses (e.g., postoperatively), cellular immunity with macrophage/microglia activation (brain abscess), antibodies to neuron cell-surface epitopes (antibody-associated encephalitis), and cytotoxic T-cell injury (paraneoplastic encephalitis). Effects on hemostasis due to regional vasodilation or vasoconstriction (as in sepsis) commonly lead to hypoperfusion and, subsequently, oxidative stress.

[b]These neurophysiologic disruptions accompany many types of delirium and may involve certain "final common pathways." It is unclear whether there are precipitant-specific subtypes that uniquely represent these pathophysiologic states.

need to be balanced with the understandable risk of polypharmacy and potential for adverse effects.

Current management of delirium involves "treating the underlying cause" (i.e., addressing delirium precipitants), managing delirium with an emphasis on its associated psychiatric symptoms, and promoting procognitive factors with nonpharmacologic interventions (see Figure 1). It bears repeating that most agents, such as neuroleptics, used to "treat delirium" are intended to "manage" its psychiatric symptoms. In most instances, there is only indirect evidence that these agents correct underlying neurophysiologic alterations, and their effect on specific types of neurophysiology and procognitive factors is theoretical at best.

A delirium disorder typology based on neurophysiology would complement current approaches by offering the opportunity to target specific delirium neurophysiology as well. It also may allow clinicians to manage delirium where a precipitant is not immediately identified (e.g., treating associated noradrenergic overactivity), when no clear precipitant is identified despite thorough evaluation,[91] or when persisting neurophysiologic disruption propagates delirium even after the index insult has passed (e.g., postoperative inflammation which presents after index tissue injury[92]). Further, it may prevent neurophysiologic insults from leading to permanent neuropathologic sequelae (e.g., persistent hypoxia leading to demyelination[93]).

A pathophysiologically informed approach to delirium disorder may also elucidate how delirium contributes to neuropathology and associated long-term impairment. We cannot overemphasize that delirium itself should not be implicated as the cause of long-term sequelae and that we ought not to presume that by preventing delirium we have ipso facto prevented a neurophysiologic process that leads to neuropathology. We should also be vigilant for the potential paradox where we have prevented delirium but worsened outcomes (e.g., interventions might blunt phenotypic manifestations, rather than alter underlying neurophysiologic changes). Merely preventing delirium may lead us to overlook otherwise quiescent biological insults or miss subtle neurophysiologic disruption causing indolent, accumulating neuropathology. That is, we might save the canary while poisoning the coalminers.[76]

Our transtheoretical model with proposed neurophysiologic subtypes offers several directions for future research. Principally, though, our typology is provisional and requires validation. Homogeneous cohorts (e.g., postcardiotomy delirium, hepatic encephalopathy) are likely to limit statistical variance and allow for more targeted validation studies. For instance, are there biomarkers or functional imaging findings that reliably define specific neurophysiologic subtypes? The provisional nature of our typology is also invitation for further refinement. As neurophysiologic subtypes are validated, a generation of studies ought to evaluate the efficacy of theorized translational interventions. In fact, future delirium intervention studies would do well to assess biologically plausible biomarkers to define the delirium disorder subtypes that respond to such interventions. It is not unreasonable to envision a future where bioassays, such as specific cytokine levels or patterns, a dexamethasone suppression test, or peripheral cholinesterase activity, are routinely assessed in delirium and meaningfully inform care.

CONCLUSION

There is an urgent need for a clearer understanding of delirium disorder as well as effective treatments for this all too common, disabling condition. Several factors have served as formidable barriers to developing effective delirium treatments and making definitive clinical advance; among these include delirium's diverse clinical features, the broad scope of delirium precipitants, the potential for confounded outcomes in medically ill and medically complex cohorts, and even the varied meanings of the word delirium itself.

Our proposed model of delirium disorder, itself composed of interactive elements, does several things: 1) it allows for univocal differentiation between delirium disorder and the clinical phenotype of delirium; 2) it proposes and highlights delirium neurophysiology as a largely unexplored treatment target; 3) it differentiates the core features of delirium from associated psychiatric symptoms; 4) it suggests "how" procognitive factors influence the elements of delirium disorder, thereby providing biological rationale for their effect; and 5) it allows for mechanistic predictions about the relationship between the elements of delirium disorder and subsequent cognitive impairment. We pair this model with a preliminary delirium disorder typology based on candidate neurophysiologic disturbances, which may provide a much needed roadmap for progress and allow us to apply modern neuroscience to this disease of antiquity.

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