Delirium: Sifting Through the Confusion

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Delirium is commonly encountered in the hospital setting, particularly in the intensive care unit. However, the diagnosis is often missed, due in part to the nature of the illness, fluctuating levels of consciousness, and varied presentation. Even when it is recognized, delirium can be hard to manage, with multiple factors contributing to its course. In this article, we review the latest information regarding the underlying mechanisms of the syndrome and treatment options available. This is accomplished by examining two complex cases encountered at a university medical center–based psychosomatic service.

Introduction

The concept of *delirium* has been around for millennia. Derived from Latin (*de* meaning "away from," *lira* meaning "furrow in a field," and *ium* meaning "singular"), the term literally means "going off the plowed track" or "deviating from a straight line" [1,2••]. The word itself was first used by the Roman writer Celsus in the first century AD to describe mental disorders experienced during fever or head trauma. However, Hippocrates used *phrenitis* and *lethargus* in 500 BC to describe similar symptoms—terms that are reminiscent of our current concepts of hyperactive and hypoactive delirium, respectively [3].

Despite a long history of awareness of this illness, our understanding of delirium is still suboptimal. Better knowledge about delirium is imperative, as the costs related to this syndrome are high. It is estimated that delirium complicates 10% to 25% of all acute hospital admissions, affecting up to 50% of hospitalized older patients and 60% to 85% of intensive care unit patients. Worse yet, the diagnosis of delirium is often missed, with up to 70% of cases going unrecognized by physicians [4,5]. In addition, as few as 15% of delirious patients return to their functional baseline by time of discharge from the hospital, and less than 45% show full recovery at 6 months postdischarge. This not only leads to increased length of hospital stays—from 5 to 10 days—but increased level of care needed at discharge. The total economic burden of delirium is estimated at $152 billion per year in the United States [2••]. The most troublesome statistic, however, is the high mortality rate of patients with delirium. In the hospital, mortality rates of patients with delirium range from 22% to 76%. Up to 40% of delirious patients who survive to discharge die within 1 year [6•].

An example of our limited understanding of delirium is the fact that the most widely used therapeutic agents for this syndrome were not chosen based on specific neuroreceptor targets, but rather for their ability to produce sedation and "neuroleptization" [7•,8]. Ironically, partially because of the mechanisms of these treatment modalities, many significant insights into this condition have occurred within the past 10 years. Using two case reports, we attempt to provide not only an overview of current delirium management and pitfalls but also of new understandings in the pathoetiology of this condition.

Case 1–1

A 66-year-old woman with a history of bipolar disorder was admitted to a university medical center for a chronic obstructive pulmonary disease exacerbation and pneumonia. She experienced a rapid decline in her respiratory status and required intubation, mechanical ventilation, and a steroid burst. Her mental status deteriorated by the second hospital day and was characterized by variable agitation and somnolence. Her agitation was severe enough that the primary team added haloperidol, midazolam, morphine, alprazolam, and eventually a propofol drip to her outpatient regimen, which included bupropion, fluoxetine, quetiapine, and valproate (VPA). Of note, serum ammonia was initially found to be 84 μmol/L and later increased to 92 μmol/L.

The presentation of this patient is classic for delirium, which is defined as an acutely developing mental syndrome with impairment in cognitive functions, fluctuating levels of consciousness, changes in psychomotor activity, and disturbances of the sleep–wake cycle [9]. Risk factors usually involve an interplay of predisposing and precipitating factors, including advanced age, multiple medical conditions, polypharmacy, hypoxia, dehydration, sleep deprivation,

substance withdrawal, and preexisting cognitive impairment. Approximately 25 risk factors have been identified, and having three or more present simultaneously increases the odds of developing delirium to 60% [4].

Looking specifically at this patient, multiple predisposing and precipitating factors are present. Studies have shown that every year past age 65 increases the risk of delirium by 2%. This is independent of other factors but is significantly worsened in the presence of severe medical illness. In fact, when measuring severity of medical conditions with the modified Acute Physiology and Chronic Health Evaluation II scale, the risk of delirium increases by 6% for every one-point increase in score, plateauing at a score of 18 [2••]. Polypharmacy, with three or more medications used, particularly with psychoactive (sedative, analgesics, corticosteroids, chemotherapeutic agents, and NSAIDs) or anticholinergic medicines, significantly increases delirium risk [2••,5]. While certain psychiatric diagnoses, including bipolar disorder, schizophrenia, and substance abuse, have been associated with a higher incidence of delirium, it is also possible that clinicians may incorrectly attribute agitated behavior to other premorbid psychiatric illness and underdiagnose delirium in patients with a history of psychopathology [2••].

Mechanical ventilation and delirium have a strong association, with up to 80% of mechanically ventilated patients developing delirium, which consequently prolongs the course of mechanical ventilation [4,10••]. One prominent reason may be that 90% of these patients receive benzodiazepines (BZDs) and/or opioids for sedation and to ease the discomfort associated with intubation. Both of these classes of pharmacologic agents are strongly associated with the precipitation of delirium, with opioids blamed for nearly 60% of delirium cases in advanced cancer. The mechanism by which this occurs is not completely clear, but an increase in dopamine (DA) and glutamate with a concomitant decrease in acetylcholine (ACh) has been postulated [10••]. Multiple sources also indicate that certain opiates, particularly meperidine, may be more deliriogenic than others [2••]. Some promising reports indicate that preemptive gabapentin use improves analgesia and reduces opioid needs after surgery, which would in turn lead to a potential decrease in delirium incidence [7•].

BZDs, which are γ-aminobutyric acid (GABA)-receptor agonists, are thought to lead to delirium through multiple routes: 1) interference with physiologic sleep patterns; 2) a centrally mediated ACh deficiency; 3) enhancement of *N*-methyl-D-aspartate–induced neuronal damage; 4) disruption of the circadian rhythm and melatonin release; and 5) disruption of the filtering ability of the thalamus, leading to sensory overload and hyperarousal [10••,11]. GABAergic medications paradoxically can both improve and worsen delirium. Multiple studies have shown that they are an independent risk factor for the development of delirium and can worsen delirium symptoms when used on their own to control agitation. However, they are the treatment of choice in alcohol or sedative withdrawal delirium [7•]. Dexmedetomidine, a novel sedating agent, has shown promising results in achieving sedation with significantly less risk of delirium and may prove to be a useful alternative to GABAergic medications [12].

Disruption of the sleep–wake cycle is critical to the development of delirium, with studies showing that sleep deprivation leads to impairment in memory, attention, and reaction time, as well as emotional imbalance and even psychosis. On average, intensive care unit patients get less than 2 hours of sleep in a 24-hour period. Factors associated with this decrease in sleep include repeated therapeutic interventions, diagnostic procedures, pain, fear, and a noisy environment [10••]. Although they are used for sedation, BZDs disrupt the sleep–wake cycle by disrupting physiologic sleep patterns (eg, reducing slow-wave and rapid eye movement sleep and increasing cortical activity at low doses). Melatonin, which is important for normal sleep–wake cycles and even for adapting to stress, has been shown to be decreased in delirious patients, especially the hyperactive type. Whether this is because of the direct effects of sedative agents is unclear, but melatonin supplementation and even light therapy have been proposed as treatments for the sleep symptoms, which in turn should improve delirium [10••,13,14].

The other major risk factor that our patient experienced is hypoxia. Although she was quickly intubated and placed on mechanical ventilation, even brief periods of hypoxia have been correlated with delirium. Specifically, one study showed that decreased oxygen saturation on the day of surgery was strongly linked to decreased mental function on postoperative days 3 and 7. Delirium also can be induced in healthy individuals by dropping PaO_2 to 35 mm Hg [10••]. Although the exact mechanisms are unclear, it is thought that hypoxia leads to delirium through an inability to maintain ionic gradients, particularly Ca^{2+}, which in turn leads to an increase in several neurotransmitters, namely DA and glutamate. DA is also increased because of the body's inability to convert it to norepinephrine, a process that is oxygen dependent. Additionally, hypoxia leads to reduced synthesis of ACh via disruption of the acetyl coenzyme A pathway [2••,10••]. Increased DA and reduced ACh have long been proposed as primary etiologies through which delirium occurs [9].

Yet another precipitating factor for delirium that our patient experienced was her elevated serum ammonia. VPA has been shown to lead to hyperammonemic encephalopathy independent of an increase in other liver-associated enzymes [15]. How elevated ammonia leads to delirium is still not completely elucidated, but it is believed that excessive *N*-methyl-D-aspartate receptor activation and decreased availability of cyclic guanosine monophosphate play a role. Increased GABA activity also has been implicated in hepatic encephalopathy, a fact shown when flumazenil, a BZD antagonist, was useful in treating delirium in cirrhotic patients [10••]. Finally, hepatic

Table 1. Theoretical neurochemical imbalances occurring in delirium subtypes*

Neurotransmitter	Hypoactive subtype	Hyperactive subtype
Acetylcholine	Decreased	Decreased
Dopamine	Increased	Increased
Serotonin	Decreased (anoxia, infection, and systemic illness)	Increased (serotonin syndrome)
	Increased (hepatic failure)	
Tryptophan	Increased (anoxia, hepatic failure, and infection)	Decreased (alcohol withdrawal)
	Decreased (trauma and postoperative)	
γ-aminobutyric acid	Decreased (anoxia)	Decreased (alcohol withdrawal)
	Increased (hepatic failure)	
Glutamate	Increased (hepatic failure)	Increased (alcohol withdrawal)
Melatonin	Increased (increased somnolence)	Decreased (sleep deprivation)
Norepinephrine	Decreased (anoxia and hepatic failure)	Increased (alcohol withdrawal)
Cytokines	Increased (anoxia, infection, dehydration, and postoperative)	Possibly increased

*Causes listed in each subtype heading are those most often associated with that subtype, but each condition can lead to different subtypes in individual patients.

encephalopathy also has been shown to increase levels of tryptophan and serotonin (5HT). As with GABA, both increased and decreased levels of 5HT have been found in delirious patients [13].

Case 1–2

The Psychosomatic Medicine (PSM) service was consulted when the primary team was having difficulty weaning the patient off propofol. She continued to have episodes of severe agitation that included pulling at intravenous lines, fighting the ventilator, and attempted self-extubation, followed by episodes of extreme somnolence. The PSM service initially recommended discontinuation of her bupropion and fluoxetine but continued use of quetiapine and VPA. The patient's steroids were rapidly titrated off because of concerns that this was increasing her agitation. VPA was also soon discontinued because of persistently elevated ammonia.

Subtyping of delirium is an important consideration because of possible different etiologic considerations and because it affects prognosis and treatment [16•]. Three subtypes have been described: hyperactive, hypoactive, and mixed presentations. Hyperactive patients are typically restless, agitated, and hyperalert and often experience hallucinations and delusions. These patients can be confused with manic or psychotic individuals. Hypoactive patients, on the other hand, often appear lethargic and drowsy, are slow to respond to questions, and demonstrate psychomotor slowing. Hypoactive delirium is often confused with depression or dementia. The mixed subtype appears, as the name implies, with a mix of hyperactive and hypoactive symptoms [17].

It is believed that the hypoactive form of delirium is the most prevalent, followed by the mixed and hyperactive forms, although there is some debate regarding prevalence of the latter two [4]. A study looking specifically at subtype incidence in mechanically ventilated patients found that up to 75% developed delirium, with 65% having the hypoactive subtype, 6% to 9% having the mixed subtype, and 1% having the purely hyperactive form [18]. Because of the fluctuating psychomotor levels from agitation to retardation, our patient was most likely experiencing the mixed subtype. The purely hyperactive form of delirium, which is usually promptly referred to psychiatry service, appears to have the best prognosis [4]. Each subtype also has been linked to different etiologic factors. Hypoactive delirium has been linked to hypoxia, metabolic disturbances, and anticholinergic medications; the hyperactive form is associated with alcohol and drug withdrawal, drug intoxication, and adverse effects of medications [17]. Finally, altered levels of various neurotransmitters have been postulated to play a role in each subtype, including DA, ACh, tryptophan, 5HT, and melatonin (Table 1) [3,10••,13,14,19].

Case 1–3

As agitation persisted, multiple treatments were attempted. Haloperidol was titrated to 15 mg intravenously every 8 hours plus some as-needed doses. Quetiapine was increased to 200 mg twice daily and 400 mg at night. Eventually, propofol was discontinued, but the agitation resumed, at which time risperidone, 1 mg every 6 hours as needed, was added to the regimen. Sometime after the addition of risperidone, a new type I atrioventricular nodal blockade and QTc prolongation of 462 msec developed. Quetiapine, risperidone, and haloperidol were stopped, and olanzapine was initiated at 5 mg three times daily, with 5 mg every 6 hours as needed. Unfortunately, after olanzapine was titrated up, the patient developed severe extrapyramidal symptoms (EPS). Quetiapine was restarted with close monitoring of

the patient's QTc. After nearly 5 weeks of treatment and continued failure to wean from the ventilator, the patient received a second course of corticosteroids. This resulted in a significant decrease in distress during weaning trials and eventual extubation. Over the next few days, the patient's delirium cleared. She was discharged from the hospital on a combination of quetiapine and lithium.

The identification and treatment of the underlying systemic medical causes is crucial in delirium management. In this case, the patient only experienced relief from her delirium once her respiratory status improved. In addition to actively managing medical causes of delirium, clinicians can practice "multicomponent" treatments described by Inouye [6•] and Fick et al. [20] that can decrease the incidence of delirium and minimize its severity through awareness of risk factors and avoidance of precipitants.

There are no US Food and Drug Administration–approved medications for the treatment of delirium, but antipsychotics are usually considered the first-line agents, particularly for the hyperactive and mixed subtypes, in which agitation and psychosis can lead to dangerous behavior and caregiver distress. However, hypoactive delirium has also been shown to benefit from antipsychotic use [16•]. The choice of antipsychotic should be based on presenting symptoms, the underlying etiology, and comorbid systemic medical conditions. For example, hyperactive delirium may benefit more from sedating antipsychotics, while patients with prolonged QTc or poorly controlled diabetes mellitus may benefit from agents that have less impact on these conditions (Table 2) [4].

Haloperidol is the best studied agent, although its use has declined in recent years with the advent of second-generation antipsychotics (SGAs). One reason for this is the concern for EPS, although EPS risk with haloperidol is believed to be significantly reduced when using the parenteral forms. Intravenous use of haloperidol also has minimal effects on blood pressure, respiration, and heart rate. There has been concern about an increased risk of QTc prolongation and torsades des pointes, although total risk is thought to be relatively low (< 1%) [2••]. Hypokalemia and hypomagnesemia have been associated with prolonged QTc; checking their values and obtaining a baseline QTc is recommended. Reasons to limit intravenous haloperidol use include baseline QTc greater than 440 msec in conjunction with other QTc-prolonging medications or a 25% increase in QTc value from baseline [2••]. Additionally, many SGAs can prolong the QTc interval to a greater extent than haloperidol [21].

SGAs have gained favor over the past several years because of their potential for lower EPS and tardive dyskinesia. It is interesting to note that our patient experienced EPS after switching exclusively to olanzapine, not while on quetiapine, risperidone, and haloperidol. This may have been because of lower EPS risk with intravenous haloperidol and quetiapine and because risperidone was primarily an as-needed medication in her case. Additionally, specific areas of the brain are more susceptible to hypoxic injury, including the basal ganglia, which may have predisposed our patient to EPS [10••]. When looking at the incidence of EPS side effects between low-dose haloperidol (< 4 mg/d) and SGAs, the Cochrane review concluded that they were comparable [22].

Evaluating the overall effectiveness of SGAs, multiple case reports and small studies have demonstrated the utility of all these agents in delirium [7•,23,24]. Further attempting to quantify the usefulness of these agents, pooled data have shown that risperidone is effective in treating approximately 85% of delirium cases, and olanzapine in up to 76% of cases. Of all the SGAs, olanzapine was shown to have the most significant side effects, with at least one study showing decreased effectiveness in hypoactive delirium [10••]. The Cochrane review concluded that studies to date had not shown the efficacy of SGAs to be superior to that of haloperidol [22]. Additionally, there have been some reports on prophylactic antipsychotic use. Early trials with preoperative haloperidol use showed a reduction in delirium severity and duration but not in incidence. However, recent studies with prophylactic use of risperidone and olanzapine have demonstrated significant benefit in decreasing incidence, duration, and severity of delirium episodes [7•].

In 2005, the US Food and Drug Administration issued a black box warning on SGAs, citing a 1.6- to 1.7-fold increased risk of death in older adult patients with dementia treated with these medications, with cardiovascular events and infections being the leading causes [21]. Recently, studies have called into question these results, demonstrating increased rates of hospitalization and death among demented patients who were nonusers of antipsychotics compared with those of users. In addition, antipsychotics are thought to indirectly increase the ACh levels in the brain due to the inverse relationship between DA and ACh. Thus, they may play a greater role in correcting underlying neurotransmitter imbalance than previously believed [2••,10••]. However, a recent study concluded that serious events are frequent with short-term use of antipsychotics in older demented patients [25]. With all the conflicting data present, a careful weighing of the risks versus benefits when using antipsychotics is necessary, and it is important to use the lowest dosages for the minimum time required. It is generally recommended that antipsychotics be continued 7 to 10 days after delirium resolves, and then discontinued [4].

Case 2–1

A 43-year-old man was involved in a tractor accident from which he incurred multiple injuries, including an epidural hematoma, subarachnoid hemorrhage, right frontal intraparenchymal hemorrhage, skull fractures, and facial fractures. His initial Glasgow Coma Scale score was 13 but soon dropped to 7. Toxicology screens were positive for alcohol and amphetamines. Early in his hospital stay,

Table 2. Benefits and risks associated with medication use in delirious patients

Drug	Benefits	Risks
Haloperidol	Most studied agent	EPS (especially in oral and intramuscular formulations)
	High potency	Neuroleptic malignant syndrome
	Multiple routes of administration	QTc prolongation (especially with IV formulation)
	IV formulation has less EPS risk	Can impair cognitive recovery
	No active metabolites	
SGAs	Less EPS risk	Increased risk of death in older adults (cerebrovascular accidents, infections)
Risperidone	Most studied and best efficacy of SGAs (85% success rate)	Higher risk of EPS than other SGAs
	Moderately sedating	Hypotension
	Dissolvable tablet form available	Higher risk of QTc prolongation
		To be avoided in patients with severe renal impairment
Olanzapine	Sedating for agitated patients	Higher anticholinergic potential
	Intramuscular and oral formulations available	Greater metabolic side effects
	Dissolvable tablet form	Less effective in hypoactive subtype
	Less QTc risk	Excessive sedation in some patients
Quetiapine	Sedating for agitated patients	Modest metabolic side effect potential
	High serotonin and modest dopamine-2 activity	Modest risk of QTc prolongation
Ziprasidone	Less sedating for hypoactive patients	Limited reports on effectiveness
	Significantly fewer metabolic side effects	Higher QTc prolongation risk
	Intramuscular formulation available	
Aripiprazole	Unique mechanism of action	Limited evidence for effectiveness
	Least risk of QTc prolongation	Can be activating
	Fewer metabolic side effects	Higher incidence of akathisia
	Less sedating potential in hypoactive subtype	
	Rapidly dissolving form available	
Benzodiazepines	First-line agents for treatment of sedative/alcohol withdrawal	Can worsen other causes of delirium
	Adjunct role in controlling agitation	Paradoxically worsen agitation
		Disrupt sleep–wake cycle
Anticonvulsants	VPA often used for agitation	VPA: hyperammonemia, thrombocytopenia, and liver dysfunction
	CBZ, OXC, and VPA useful in alcohol withdrawal	CBZ: hyponatremia, aplastic anemia, rash, and possible cardiac conduction abnormalities
	Proposed mechanism of action can correct deficiencies	
	Proposed for use in treatment of delirium (ie, serotonin activity, Ca^{2+} gradient, and γ-aminobutyric acid)	
Serotonin agents	Serotonin increase and decrease proposed in delirium	Not well studied
	Ondansetron (serotonin antagonist) showed benefit in controlling behavioral agitation	Unclear in which conditions serotonin is increased or decreased
	Trazodone has shown some benefit	

CBZ—carbamazepine; EPS—extrapyramidal symptoms; IV—intravenous; OXC—oxcarbazepine; SGA—second-generation antipsychotic; VPA—valproate.

Table 2. Benefits and risks associated with medication use in delirious patients (*Continued*)

Drug	Benefits	Risks
Melatonin	Natural agent found to have strong correlation with sleep–wake cycle	Limited studies associating melatonin levels with delirium
	Decreased levels found in hyperactive patients	No agents studied in treatment
Dexmedetomidine	Novel α2 agonist sedating agent	Small number of studies
	Sedation with less risk of delirium	Not widely used
Psychostimulants	Useful in activating hypoactive patients	Can lead to psychosis and agitation

CBZ—carbamazepine; EPS—extrapyramidal symptoms; IV—intravenous; OXC—oxcarbazepine; SGA—second-generation antipsychotic; VPA—valproate.

he required a brief period of intubation due to loss of consciousness. After extubation, the patient became combative and agitated. Intravenous haloperidol was started by the primary trauma surgery team. However, within a few days, new-onset bradycardia and sinus pauses were noted, requiring discontinuation of the haloperidol.

Traumatic brain injuries (TBIs) are strongly associated with acute and long-term behavioral and cognitive impairment, with greater severity of the injury linked to greater impairment. The degree of severity is not associated with the nature of the injury but instead to the Glasgow Coma Scale score, with a score of 3 to 8 defined as severe. Delirium is also common in moderate to severe TBI, as it is the second step in a five-stage process known as post-traumatic encephalopathy [26]. The mechanisms by which delirium is induced are similar to what has been previously discussed, including neurotransmitter imbalance, cytotoxic injury, and diffuse axonal injury. Whatever the mechanism, an imbalance of ACh and DA appears to be instrumental, and agents that can correct this imbalance are key to treatment [10••,26].

The other important point of discussion with TBI is the associated long-term cognitive impairments that can occur. Approximately 35% of patients with moderate to severe TBI have lasting cognitive, physical, and behavioral impairments that may put them at greater risk for future delirium episodes [20,26]. There has been a strong correlation between cognitive impairments (eg, dementia) and the risk of delirium. Several studies have shown that the prevalence of delirium superimposed on dementia is greater than 50%, with most cases being the hypoactive subtype. As noted with TBI patients, dementia and delirium share many pathophysiologic features, including cholinergic deficit, decreased cerebral metabolism, diffuse axonal injury, and an inflammatory response [20,27]. Additionally, delirium contributes to worsening functional status in patients with preexisting dementia, dramatically worsening the course of cognitive decline and possibly doubling the mortality rate [6•,20]. The concept of a "delirium-prone brain" is important to understand, as preexisting underlying cognitive vulnerabilities can leave patients more susceptible to future episodes of delirium than the general population.

Case 2–2

The PSM service was consulted for assistance with management of agitation. On initial evaluation, the patient was angry, confused, using profanity, and generally speaking incomprehensibly. His vital signs remained stable, and no diaphoresis or tremors were noted, moving alcohol withdrawal lower on the differential. By hospital day 8, he was started on VPA, 500 mg twice daily, and olanzapine, 5 mg orally or intramuscularly twice daily, with an additional 5 mg every 6 hours as needed. Eventually, intravenous VPA was started because of patient nonadherence, but this was discontinued due to an elevated ammonia of 140 μmol/L. In time, the oral formulation was restarted with the addition of lactulose and L-carnitine, which helped to reduce the ammonia to 64 μmol/L. Olanzapine was increased to 10 mg twice daily, but this was switched to quetiapine because of suspected akathisia. However, the quetiapine, dosed up to 200 mg, was also discontinued secondary to hypotensive episodes. By hospital day 25, the patient appeared to be gaining more insight into his condition, understanding that he had been in a severe accident and had significant memory impairment. He continued to exhibit impulsive behavior, at one point attempting to use his restraints to hop his bed out of the room. However, with continued treatment, his Mini-Mental State Examination score improved to 27, and he was exhibiting improved judgment and impulse control, which allowed him to be safely discharged to the care of his family.

The use of antipsychotics to treat delirium was discussed extensively in the previous case. However, there are a few other important considerations to note. First, post-TBI delirium should be treated with agents that are less specific DA_2-receptor antagonists due to observations that haloperidol can slow cognitive recovery [4]. Despite no such formal recommendations being made in dementia patients, studies have shown minor improvements in some cognitive functions of dementia patients taking quetiapine versus haloperidol [28]. Although a nonpharmacologic approach to the care of delirious patients, especially those with underlying cognitive impairment, is recommended, current evidence for its effectiveness is mixed [4,20].

In light of the unclear value of nonpharmacologic approaches and the multiple potential consequences associated with antipsychotics, alternative treatment strategies

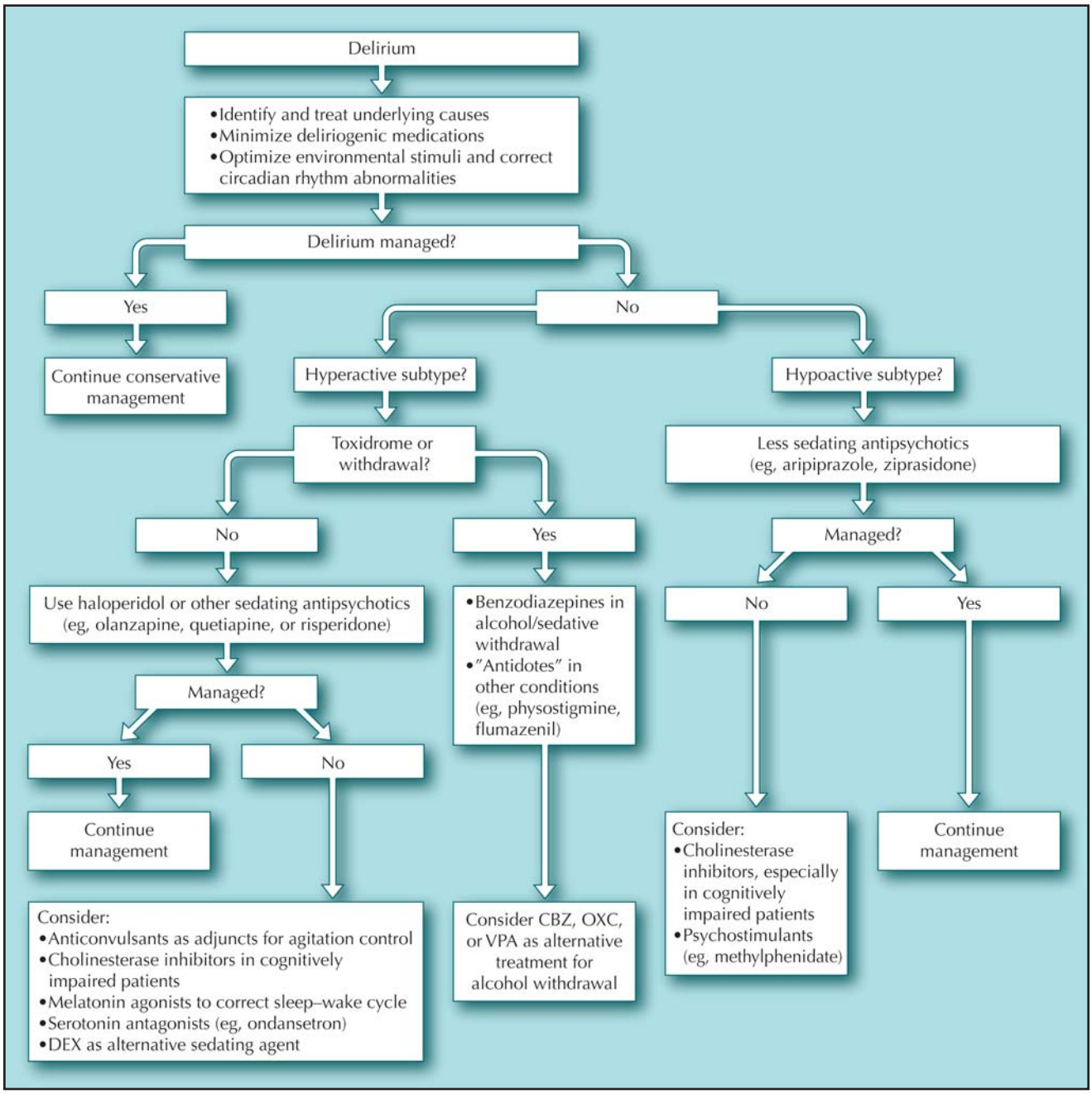

Figure 1. Proposed algorithm for the treatment of delirium. CBZ—carbamazepine; DEX—dexmedetomidine; OXC—oxcarbazepine; VPA—valproate.

are required for the management of delirium (Fig. 1). Anticonvulsants have long been used to control agitation and aggression in psychiatric disorders and in dementia. In fact, the use of VPA is recommended for the control of neurobehavioral symptoms of TBI patients [26]. In addition, several anticonvulsants (eg, carbamazepine and VPA) can help to regulate sodium and calcium fluxes, modulate serotonin (VPA), and facilitate GABA inhibitory transmission, all of which are thought to play a role in delirium etiology [10••,29]. Indeed, there is growing evidence that carbamazepine, oxcarbazepine, and possibly VPA are useful in the treatment of alcohol withdrawal and potentially the delirium associated with it [29]. There have been no definitive studies looking at the use of anticonvulsants in the management of delirium, although a small number of case reports have described VPA as a useful adjunct [30].

With our current understanding of the mechanisms of delirium, it would seem clear that cholinesterase inhibitors should play an integral role in the management of this syndrome. Many case reports have shown dramatic improvements in patients with delirium who were given cholinesterase inhibitors [8]. A study looking at rivastigmine, a dual inhibitor of acetylcholinesterase and butyrylcholinesterase, in vascular dementia patients showed a reduction in the incidence, duration, and severity of delirium episodes [10••].

However, two large-scale trials with donepezil failed to show any benefits in the prevention of delirium. The Cochrane review went on to state that there currently is no evidence to support the use of cholinesterase inhibitors in the treatment of delirium [31].

There are minimal data on the effectiveness of other agents in treating delirium. As mentioned previously, a novel sedating agent, dexmedetomidine, a selective α2 agonist, has shown promise in reducing the incidence of delirium [12]. A single case report exists on the use of ondansetron, a 5HT antagonist, in the treatment of physical and verbal agitation associated with delirium [10••,21]. Additionally, melatonin has been postulated to correct the sleep–wake cycle in patients with hyperactive delirium, thus potentially improving delirium symptoms, and BZDs and possibly anticonvulsants have a role in alcohol withdrawal states [7•,29]. Finally, psychostimulants such as methylphenidate have been found to improve cognitive and psychomotor functions in patients with hypoactive delirium, although there is a risk of aggravation and psychosis [7•].

Conclusions

Despite years of study, delirium remains poorly understood. At its core, delirium is believed to be a neuropsychiatric syndrome of disturbed consciousness and attention, altered circadian rhythm, psychomotor functions, and perceptions. Unfortunately, even with awareness of the illness, it is often missed by clinicians and explained away as a "normal reaction to being in the intensive care unit" or as symptoms of an underlying cognitive or other psychiatric disorder. Although preexisting conditions can increase the chances of developing delirium, it is important to understand that the syndrome is its own entity that requires urgent evaluation and treatment. Missed diagnosis leads to significantly increased morbidity and mortality and a substantial economic burden to society as a whole.

Considerable research still needs to be done on the pathoetiology of delirium. Our basic model of delirium as a DA excess and ACh deficiency has expanded to include other neurotransmitters, cytokines, amino acids, and ionic gradients, although much of this is still theoretical. A greater understanding of how delirium occurs will allow for better treatment options. Our current treatment regimens, although they are of some value, are fraught with perils and have limited data from large comprehensive studies to support their use. With better understanding will come better treatment, which in turn will lead to better outcomes for these very sick patients.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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