Delirium

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"Mr. A" is a 79-year-old man with type 2 diabetes, hypertension, and hyperlipidemia who was brought to the emergency department for confusion. His home health aide reports that Mr. A has increasingly been refusing his medications lately and has also refused to see his primary care physician for a nonhealing leg wound. On arrival at the emergency department, Mr. A has a temperature of 101.5°F, pulse of 126 bpm, respirations of 22 breaths per minute, and blood pressure of 79/52. Initial laboratory tests demonstrate leukocytosis (WBC 14.6), prerenal azotemia (creatinine, 2.1 μmol/L; blood urea nitrogen, 54 mg/dL), and a lactate level of 4.3 mmol/L. The patient's hemoglobin A_{1C} is 9.6%. Blood cultures show methicillin-resistant *Staphylococcus aureus* in 4/4 bottles.

On physical examination, the patient is tachycardic and tachypneic; abdominal examination is benign. Skin examination demonstrates bilateral venous stasis changes, with a large, shallow ulcer along the left tibia with dusky borders and central eschar. Mental status examination reveals a disoriented, inattentive, disheveled elderly male who is picking at his hospital gown and calling out to his wife, who is deceased. He is diagnosed with sepsis and admitted to the medicine service for further workup and treatment. A psychiatric consultation is obtained to assess the patient's mental status and assist with management of agitation.

Mr. A remained on the medical service for 6 days, during which time his sepsis was treated with intravenous antibiotics and his leg ulcer debrided and dressed. His renal function recovered with adequate hydration, and his vital signs rapidly renormalized. To address Mr. A's delirium, his nurses provided frequent reorientation regarding the date and situation and ensured that he received plenty of light exposure during the daytime while preserving a quiet, dark, minimally disturbed environment overnight. A medication reconciliation demonstrated a previous outdated prescription for meclizine for vertigo, which was discontinued given its strong anticholinergic activity and absence of active dizziness. Mr. A's home health aide brought in the patient's glasses, hearing aids, and dentures for his use in the hospital. The physical therapy department worked with the patient beginning on the second day of his admission and found him increasingly able to participate in active mobilization as his medical problems and mental status improved. The patient had orders for standing melatonin, 3 mg h.s., as well as quetiapine, 12.5 mg b.i.d. p.r.n., and he required two evening as-needed doses of quetiapine. Both medications were fully discontinued before discharge.

Mr. A was discharged to acute rehabilitation before returning home. At an outpatient follow-up appointment 6 months later, his home health aide remarked that the patient was now more forgetful and appeared cognitively slower than he had been before the infection, and that he now required around-the-clock assistance with activities of daily living.

Delirium is a syndrome of acute brain failure that is the direct pathophysiologic consequence of an underlying medical condition or toxic exposure. According to DSM-5 (1), it is characterized by the acute onset of deficits in attention, awareness, and cognition that fluctuate in severity over time. Delirium represents global brain dysfunction, and thus the cognitive impairments are highly variable, including disturbances in several domains, such as memory, orientation, language, visuospatial ability, and perception. Additional features include psychomotor disturbance, altered sleep cycle, and emotional variability. The psychomotor disturbances seen in delirium have been categorized into three phenotypic subtypes: hyperactive, hypoactive, and mixed delirium. Hyperactive delirium is characterized by psychomotor agitation, restlessness, and emotional lability and is sometimes mistaken for primary psychosis, mania, or dementia. Hypoactive delirium is characterized by psychomotor retardation, lethargy, and decreased level of responsiveness and is often missed or misdiagnosed as depression. Mixed delirium presents with alternating features of both.

CHARACTERISTICS OF DELIRIUM

Epidemiology

Delirium is the most common psychiatric syndrome observed in hospitalized patients (2). The incidence on general medical

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wards ranges from 11% to 42% (3), and it is as high as 87% among critically ill patients (4). A preexisting diagnosis of dementia increases the risk for delirium fivefold (5). Other risk factors include severe medical illness, age, sensory impairment, and male gender (5). Common deliriogenic medication classes include narcotics, hypnotics (such as benzodiazepines), and anticholinergics. The incidence of delirium is particularly high among burn patients (39%), nonelective postoperative patients (>50%), and patients receiving mechanical ventilation in the intensive care unit (ICU) (>70%) (6–8).

Diagnosis

Although delirium is common, the diagnosis relies on a high index of suspicion, as it often goes undetected or misdiagnosed. In one study, nursing staff identified delirium in only 31% of cases identified by research staff (9). In another study, up to 40% of hospitalized patients referred for a psychiatric consultation for depression were found to be delirious (10). There are multiple challenges to establishing the diagnosis of delirium in a timely fashion, including the fluctuating course of symptoms, difficulty conducting cognitive testing during the extremes of psychomotor disturbance, overlooking the hypoactive phenotype, and the need to ascertain baseline cognitive functioning. A thorough clinical evaluation is considered the gold standard for diagnosis of delirium, as there is no clinical study or biomarker with high sensitivity and specificity. Although EEG studies typically show generalized slowing in delirium, the false negative and false positive rates approach 20%, limiting the utility of this tool (11). Multiple validated delirium screening tools with high sensitivity and specificity have been developed, including the Confusion Assessment Method and the 4AT rapid clinical test for delirium, which improve the detection of delirium by a variety of health care professionals (12, 13).

Differential Diagnosis

Delirium in medically ill patients is often multifactorial, and while attention is importantly given to broad surveillance and monitoring of contributing variables, the role of the psychiatric consultant often involves focusing specifically on potential neuropsychiatric processes. Substance withdrawal may require a careful medication history to identify and clarify use patterns, even of prescribed benzodiazepines and opioids; this may also inform seizure risk assessment. Many commonly used agents, including some opioids, antinausea medications, antimigraine medications, mood stabilizers, linezolid, and ritonavir, have serotonergic activity. A careful medication history can clarify the risk of serotonin syndrome, particularly in patients on standing serotonergic medications who then require additional serotonergic agents to address acute medical issues. A broader differential diagnosis can be considered in the context of the patient presentation at the time of consultation. Immunosuppression increases the risk for opportunistic CNS infections, including herpes simplex virus encephalitis, as well as various cancers that may metastasize to the brain; severe metabolic derangements may prompt consideration of paraneoplastic syndromes, central pontine myelinolysis (following rapid correction of hyponatremia), hyperammonemia, and seizure; coagulopathies, atrial fibrillation, and endocarditis predispose for stroke; and extreme hypertension may trigger consideration of posterior reversible encephalopathy syndrome and stroke. In addition to the CNS etiologies of delirium mentioned above, other common etiologies include infection, reduced sensory input, urinary retention or fecal impaction, metabolic derangements, and myocardial or pulmonary disorders. Further investigation for these etiologies would depend on the patient's clinical presentation and the results of screening laboratory tests.

While scope of practice may vary with training experience, it would be reasonable to recommend a neurologic consultation when there are focal neurologic findings, including any new asymmetry on physical examination, movement abnormalities, sustained poor mental status (concerning for status epilepticus), and abrupt deterioration in mental status after a period of delirium previously marked primarily by inattention and disorientation.

Impact of Delirium

While delirium has historically been viewed as a time-limited disorder, the morbidity (both short- and long-term), mortality, and financial costs are increasingly being recognized. A meta-analysis of delirium in the elderly showed that even after controlling for confounding factors, including age, sex, dementia, comorbid illness, and illness severity, delirium is independently associated with a twofold increase in risk of death, a 2.4-fold increase in risk of institutionalization, and a 12.5-fold increase in risk of dementia (14). Delirium has also been strongly associated with sustained decline in physical function, with the average loss of one activity of daily living per delirious episode, sustained at 6-month follow-up (15). In patients with and without dementia, multiple symptoms of delirium have been shown to persist for 12 months after the onset of delirium (16). In addition to significant patient mortality and negative functional outcomes, delirium is also associated with high health care costs. On average, hospital stays are 5–10 days longer for patients who develop delirium than for patients without delirium (2). A 1-year prospective study found that patients with delirium had significantly higher unadjusted health care costs than patients without delirium. After adjusting for demographic and clinical factors, the cost of treating a patient with delirium was 2.5 times that of a patient without delirium, and the annual national burden of delirium is estimated to be in the range of $38 billion to $152 billion (17).

Pathophysiology

While the pathophysiologic basis of delirium has yet to be fully elucidated, delirium can be conceptualized as a final common pathway resulting from multiple factors that lead to a state of impaired brain function. Inflammation, hypoxia, and oxidative stress all contribute to increased brain exposure to toxins and a hypocholinergic-hyperdopaminergic state. Inflammation creates a vulnerable physiological state, with impaired brain

function and increased permeability of the blood-brain barrier. Susceptibility to circulating deliriogenic medications, endogenous toxins, and proinflammatory cytokines may cause or sustain delirium (18). Microaggregates of fibrin and neutrophils in the cerebral vasculature can cause subclinical episodes of decreased cerebral perfusion, particularly in patients with high vascular disease burden (19). Subclinical transient hypoxic states lead to decreased synthesis of acetylcholine, the primary neurotransmitter of the reticular activating system. The reticular activating system is primarily involved in regulating alertness and attention, the disruption of which are a hallmark of delirium (20). Because intact alertness and attention are a fundamental substrate for all domains of cognition, the cognitive deficits seen in delirium are diffuse and nonspecific. Thus, any specific cognitive deficits elicited on bedside testing during a delirious state should be interpreted with caution. Oxidative stress results in the release of endogenous dopamine, which is thought to be the underlying cause of perceptual disturbances seen in delirium (21). Other neurotransmitter derangements implicated in delirium include melatonin deficiency, resulting in sleep-wake cycle disruption, and excess norepinephrine and glutamate.

Brain Circuitry

Delirium is associated with aberrant resting-state neural interactions between the suprachiasmatic nucleus (the biological master clock) and cortical regions. Compared with nondelirious control subjects, in patients with delirium, functional connectivity from the suprachiasmatic nucleus is increased to the dorsal anterior cingulate cortex and decreased to the posterior cingulate cortex, parahippocampal gyrus, cerebellum, and thalamus (22). The functions of the regions showing decreased connectivity correspond with the clinical symptoms of delirium, including the role of the posterior cingulate cortex in maintaining consciousness of the external environment, the parahippocampal gyrus in memory encoding and retrieval, and the cerebellum and thalamus in mental coordination. Delirium is also associated with increased functional connectivity between the dorsolateral prefrontal cortex and the posterior cingulate cortex, as well as decreased connectivity of subcortical regions (23). Finally, aberrations in the salience network and its interaction with the default mode network and the central executive network have been demonstrated in minimal hepatic encephalopathy (24).

The association between cortical atrophy and delirium remains controversial (25–27). One study demonstrated that while Alzheimer's-related cortical atrophy did not predict delirium incidence, it was associated with greater delirium severity (27). Neurovascular changes, including white matter hyperintensities and cerebral infarcts, have been consistently associated with increased risk of delirium (25, 26). These neurovascular changes likely increase vulnerability to hemodynamic shifts during physical illness.

PREVENTION

In clinical settings with high rates of delirium, such as critical care and postoperative units, it is helpful to predict risk of delirium to inform prognosis and the risk-benefit analysis of elective surgery. The PRE-DELIRIC (PREdiction of DELIRium in Intensive Care patients) is a delirium prediction model for intensive care patients based on nine clinical and demographic factors at the time of admission, which has been validated in seven countries (28, 29). This model has an area under the receiver operating curve (AUC) >0.8, which is significantly higher than the AUC of 0.59 for nurses' and physicians' predictions, highlighting the need for validated prediction tools (29). A similar delirium prediction score (Delphi; DELirium Prediction Based on Hospital Information) developed for general surgery patients demonstrated an AUC of 0.91 (30). The utility of incorporating preoperative neuropsychologic measures, such as depression symptoms, cognitive functioning, and neuroimaging findings, as well as intraoperative parameters, into postoperative delirium risk prediction is an ongoing area of research (31).

Nonpharmacologic Strategies

Prevention is the most effective strategy for reducing the morbidity, mortality, and health care costs associated with delirium. Since the cause of delirium is typically multifactorial, delirium prevention approaches that target multiple risk factors tend to be the most effective. The Yale Delirium Prevention Trial, a randomized controlled trial, demonstrated that a multimodal nonpharmacologic strategy is feasible (87% adherence rate) and can decrease the incidence of delirium on a general teaching medical unit from 15% to 9% (32). The delirium prevention protocol in the study targeted six risk factors by focusing on orientation, early mobilization, medication reconciliation, sleep-wake cycle preservation, sensory impairment, and dehydration. This protocol has been shown to be adaptable to, and effective in, various other settings, including surgical units and nursing homes (33, 34). Environmental strategies that promote sleep consolidation, such as minimizing nighttime noise and light exposure, also contribute to delirium prevention (35). Finally, minimization of physical restraints, which allows patients to participate in early mobilization, is critical, as the use of physical restraints increases the odds of a persistent delirium threefold (36).

Prevention strategies are equally important in intensive care settings. Many of the medications used to achieve the degree of sedation and analgesia required for mechanical ventilation, including benzodiazepines, propofol, and opioids, are deliriogenic. Daily sedation interruption has been demonstrated to be safe as well as to decrease both duration of mechanical ventilation and length of stay in the ICU (37).

Pharmacologic Strategies

The use of antipsychotics for the prevention of delirium remains controversial, with both positive and negative studies in various postoperative populations, critical care populations, and general hospital settings (38–43). Interpreting the positive and negative studies is challenging, however, because of their heterogeneous populations, differing measures of delirium, and varied antipsychotic selection and dosing. In the postoperative setting,

however, there have been three meta-analyses, all of which support the use of antipsychotics for reducing the incidence of delirium (44–46). Thus, when prophylactic antipsychotic use is studied in a more homogeneous population at high risk for delirium, prophylaxis with antipsychotics appears to be helpful. This suggests that in selected clinical settings, there may be a role for the time-limited use of antipsychotics to prevent delirium. More research is needed to determine which factors predict response to antipsychotic prophylaxis. In the absence of firm evidence supporting the efficacy of antipsychotics for delirium prevention, we recommend against routine use of antipsychotics for this purpose.

The avoidance or minimization of deliriogenic medications is as important as the use of nondeliriogenic sedation agents. For example, diphenhydramine, which is often prescribed for sleep, can cause or contribute to delirium because of its anticholinergic properties.

Dexmedetomidine, a selective α_2-adrenergic receptor agonist, has been shown to reduce the incidence of delirium and ventilator-associated events while increasing ventilator-free hours (47–49). Dexmedetomidine has both analgesic and sedative properties, which allows for a reduction in the amount of deliriogenic medication exposures, including opioids and benzodiazepines. Its use can be limited by the potential for hypotension and bradycardia as well as cost.

Finally, there is a small but emerging literature to support the use of melatonin and melatonin receptor agonists (e.g., ramelteon) for the prevention of delirium in medical, surgical, and intensive care settings. Melatonin is a hormone produced by the pineal gland that helps maintain circadian rhythms and regulate sleep, the disruption of which is a known risk factor for delirium. Studies of serum melatonin levels demonstrate that the circadian secretion of melatonin is disrupted in patients who develop delirium (50). A recent meta-analysis of four randomized controlled trials assessing the preventive effect of melatonin supplementation on delirium demonstrated that melatonin showed a tendency to decrease the incidence of delirium (relative risk=0.41, 95% CI=0.15–1.13) (51). A multicenter randomized controlled trial on the impact of melatonin for delirium prophylaxis in ICUs is under way (52).

TREATMENT

Nonpharmacologic Approaches

Once delirium has developed, nonpharmacologic approaches are integral to limiting overall morbidity and mortality, including risk of long-term cognitive impairment. There is significant overlap between the nonpharmacologic strategies used in prevention and those used in treatment. These strategies target sleep-wake regulation, orientation, early mobilization, vision and hearing optimization, and nutrition and hydration. In the critical care setting, the scope of intervention expands to include daily trials of sedation reduction and spontaneous ventilation, as delineated in the ABCDEF bundle (53), an evidence-based guide for optimizing ICU patient recovery. The ABCDEF bundle's components include assessing, preventing, and managing pain; both spontaneous awakening and spontaneous breathing trials; choice of analgesia and sedation; delirium assessment, management, and prevention; early mobility; and family engagement (53). A prospective study comparing complete ABCDEF bundle performance to proportional performance (54) demonstrated that complete performance was associated with decreased risk of hospital death within 7 days (adjusted hazard ratio=0.32, 95% CI=0.17–0.62), delirium (adjusted odds ratio=0.60, 95% CI=0.49–0.72), and coma (adjusted odds ratio=0.35, 95% CI=0.22–0.56). The ABCDEF bundle is an example of a proactive, interdisciplinary approach for mitigating delirium risk factors as well as assessing for and managing delirium. Psychiatrists can play an important role in advocating for and implementing proactive, multidisciplinary prevention programs and clinical pathways within their local institutions.

There is only limited high-quality evidence in the literature addressing nonpharmacologic treatment of delirium, highlighted in a recent systematic overview in older patients (55). Both single and multicomponent protocols have undergone trials, from bright lights, earplugs, and music therapy to more comprehensive team-based approaches that can extend to family engagement (55). The evidence for multicomponent nonpharmacological interventions preventing delirium is currently much stronger than that for the treatment of already established delirium. The primary treatment of delirium is identification and management of the underlying medical etiologies, which may be highly variable within and across treatment populations, and multimodal treatment strategies to minimize the severity and duration of delirium are thus essential.

Antipsychotics

While there are no medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of delirium, antipsychotics are commonly used as a first-line pharmacologic approach to manage symptoms that threaten safety or impede care when nonpharmacologic approaches are insufficient. The efficacy of antipsychotic medications for the treatment of delirium is controversial. Although some studies suggest that the benefits of using antipsychotics outweigh the risks when used to manage specific target symptoms (e.g., agitation, paranoia, psychosis) (56, 57), a recent meta-analysis (43) found that antipsychotics demonstrated no significant effect on delirium incidence, duration, severity, length of stay, or mortality. While the current evidence regarding the effect of antipsychotics on duration of delirium is unclear, we do not yet have studies demonstrating the impact of antipsychotics on other meaningful patient measures often seen in delirium, such as emotional distress, ability to participate in care, and long-term functional outcomes.

In the absence of conclusive data, it is recommended that antipsychotic use be limited to judicious, time-limited trials for the management of high-risk and high-distress symptoms of delirium, including agitation, paranoia, and hallucinations, which pose a safety risk to the patient or staff or impede the provision of medical care (Table 1) (58). Antipsychotics can be helpful for treating clear psychotic symptoms associated with

TABLE 1. Antipsychotics and other medications used in the treatment of delirium[a]

Medication	Starting Regimen	Route	Half-Life	Maximum Daily Dose	Dosing Adjustments	Monitor for and Discontinue If Present
Haloperidol	0.5 mg b.i.d. p.r.n. for agitation or psychosis, 1 mg h.s. p.r.n. or standing (p.o. > i.v. > i.m.)	p.o., i.v., i.m.	14–30 hours	Upper limit has not been established	No renal or hepatic adjustments required	QTc prolongation, extrapyramidal symptoms, rising liver function test values, narrow-angle glaucoma, underlying Parkinson's disease or Lewy body dementia
Quetiapine	12.5 mg t.i.d. p.r.n. with 25 mg h.s. p.r.n. or standing	p.o.	6–7 hours	800 mg	No renal adjustments required; titrate slowly in hepatic impairment	QTc prolongation, orthostatic hypotension
Risperidone	0.5 mg b.i.d. p.r.n. (p.o. > ODT)	p.o., ODT	20–30 hours	8 mg	Avoid in renal impairment	QTc prolongation, extrapyramidal symptoms
Olanzapine	2.5 mg b.i.d. p.r.n. with 2.5 mg h.s. p.r.n. or standing (p.o. > ODT > i.m.)	p.o., ODT, i.m.	30 hours	20 mg	No renal or hepatic adjustments required	Avoid in patients receiving parenteral benzodiazepines
Ziprasidone	10 mg b.i.d. p.r.n. (p.o. > i.m.)	p.o., i.m.	7 hours	160 mg	No renal or hepatic adjustments required	Avoid in patients with prolonged QTc and those receiving other QTc-prolonging medications
Aripiprazole	5 mg b.i.d. p.r.n.	p.o.	75 hours	30 mg	No renal or hepatic adjustments required	Akathisia
Valproic acid	125–250 mg t.i.d.	p.o., i.v.	4–16 hours	60 mg/kg	No renal adjustments required; contraindicated in hepatic disease	Monitor platelets, ammonia, and liver enzymes
Melatonin	1–3 mg h.s.	p.o.	60 minutes	10 mg h.s.	None	May cause daytime sleepiness

[a] ODT=orally disintegrating tablet.

delirium, such as hallucinations, delusions, and paranoia. The sedative effects of antipsychotics can also be helpful for the acute management of agitation. It should be noted, however, that there is no clear evidence that antipsychotics have an impact on the core attentional or cognitive symptoms of delirium. Furthermore, it is critical that antipsychotic trials include careful monitoring for both treatment response and side effects. The selection of the antipsychotic agent may be guided by the agent's pharmacodynamic and side effect profile to maximize benefit for the unique clinical presentation. For example, patients with profound circadian disturbances and perceptual disturbances may benefit from sedating antipsychotics, such as quetiapine, dosed primarily at nighttime. Patients with hyperactive delirium characterized by rapidly escalating agitation may benefit from haloperidol, which is available in intravenous and intramuscular formulations and can be administered to patients who cannot safely receive oral medications. Patients with Parkinson's disease or Lewy body dementia are best treated with quetiapine, as first-generation and high-potency antipsychotics can worsen Parkinson's motor symptoms. If a patient with Parkinson's disease or Lewy body dementia requires a parenteral medication, intramuscular olanzapine or ziprasidone should be administered at the lowest effective dose. Individuals who are unable to swallow tablets may benefit from agents with oral disintegrating formulations, such as olanzapine and risperidone. Delirious cancer patients often benefit from the antiemetic properties of olanzapine.

In terms of dosing, as-needed daytime doses can be initiated, as well as either an as-needed or a standing bedtime dose, depending on symptom severity. Frequent use of as-needed doses should prompt initiation of standing doses at the lowest effective dose and frequency. If the patient demonstrates only partial response, doses may be gradually titrated upward, as long as daily maximum limits are not exceeded. As the patient begins to improve, standing daytime doses should be transitioned back to as-needed doses, reserving the standing bedtime dose as the last to be transitioned back to as-needed.

The three main risks associated with antipsychotic use include QTc prolongation (which increases the risk of sudden

death by torsade de pointes), extrapyramidal symptoms, and increased all-cause mortality in elderly patients with dementia. While QTc prolongation is commonly observed with antipsychotic medications, the absolute increases are modest. A study performed for the FDA by Pfizer comparing the QTc interval before and after exposure to the maximum recommended daily doses of commonly used antipsychotic medications demonstrated QTc prolongation ranging from 4.7 ms (with haloperidol) to a maximum of 20.3 ms (with ziprasidone) (59). The FDA placed a black box warning on droperidol in 2001, indicating a significant risk of QTc prolongation and cardiac arrhythmias. Many experts questioned the validity of this warning after its issuance, and a recent evidence-based review indicated that the risk of torsade de pointes is low when doses less than 10 mg are administered (60). Patients receiving antipsychotic medications during periods of delirium should have an ECG before therapy is initiated as well as after initiation to ensure that the QTc interval has not significantly lengthened. Routine monitoring of the QTc interval becomes even more critical in patients who have known heart disease and in patients receiving other QTc-prolonging medications. The incidence of torsade de pointes is 10–15 events per 10,000 person-years of observation, making it a high-risk but low-frequency incident (61). Optimization of electrolytes, particularly potassium, magnesium, and calcium, can minimize antipsychotic-associated QTc prolongation. Potassium shortens the QTc interval, and magnesium suppresses recurrent torsade de pointes without shortening the QTc interval (62).

Patients receiving antipsychotics must also be monitored for extrapyramidal symptoms, as akathisia, rigidity, and dystonias may exacerbate the underlying restlessness and disorientation seen in delirium. Akathisia is most commonly observed in patients receiving high doses of first-generation antipsychotics, although the risk of developing akathisia appears to be attenuated in patients receiving 4.5 mg/day or less of haloperidol, as well as those receiving second-generation antipsychotics (57). Patients experiencing rigidity must be monitored for the development of neuroleptic malignant syndrome, an uncommon but life-threatening condition following exposure to antipsychotic medications that is characterized by lead-pipe rigidity, elevated creatine kinase levels, fever, mental status changes, and autonomic instability (63). The differential diagnosis for neuroleptic malignant syndrome includes malignant catatonia and serotonin syndrome. The development of such symptoms should prompt immediate discontinuation of antipsychotics, as well as escalation of care to an ICU setting for close monitoring and supportive treatment, including aggressive volume resuscitation, electrolyte correction, and temperature regulation. In severe cases, additional treatment options would include benzodiazepines, dopaminergic agents, dantrolene, or electroconvulsive therapy (6–10 bilateral treatments) (64).

The FDA has issued black box warnings cautioning against the use of antipsychotic medications in elderly patients with dementia, indicating that antipsychotics are associated with increased all-cause mortality in this population (65). However, it is critical to distinguish the practice of using the lowest effective dosage of an antipsychotic for a limited period in delirious patients in a carefully monitored medical setting from the higher cumulative antipsychotic exposure observed among patient populations on which the original safety warnings were based. A subsequent study specifically examining the rate of adverse events that could be attributed to antipsychotic use among some 2,400 medical inpatients who developed delirium (66) did not find a higher mortality rate among patients receiving antipsychotics. However, a 2017 prospective placebo-controlled study of elderly patients receiving palliative care (67) demonstrated a higher survival rate among patients receiving placebo than among those receiving haloperidol. Additional multicentered, placebo-controlled studies are necessary to elucidate the risks and benefits of antipsychotic therapy in patients with delirium, as it is difficult to generalize these findings to the larger, heterogeneous, nonpalliative patient population. It cannot be emphasized strongly enough that patients receiving antipsychotics to target symptoms of delirium while in the hospital must either be fully tapered off of those agents before discharge or must have a clear discontinuation plan, as it is not uncommon for these medications to be inadvertently continued indefinitely after discharge.

Non-Antipsychotics

Antiepileptics. Valproic acid has shown promise in case series and retrospective cohort studies for the treatment of delirium (68, 69). Postulated mechanisms of action include modulation of a range of neurotransmitters (GABA, dopamine, glutamate, acetylcholine) and increasing melatonin levels (70). Valproic acid may be administered orally or intravenously, and it may provide secondary benefits for delirious patients with comorbid alcohol withdrawal, history of traumatic brain injury, or mood disorder. Loading doses are often, but not uniformly, utilized. In a recent retrospective study, the median dosage was 23 mg/kg per day in divided doses (68). While serum levels are useful to identify toxicity, to achieve effect for delirium, serum levels need not reach the range of 50–125 μg/mL recommended for management of mood instability. Valproic acid should be avoided in patients with significant hepatic or pancreatic dysfunction, patients with active bleeding or a low platelet count, and pregnant patients. Blood counts and liver enzyme levels should be obtained before initiating valproic acid and then monitored. Ammonia levels should be monitored, as hyperammonemia can contribute to hepatic encephalopathy, confusing the presentation of delirium. Once agitation has remitted, a taper schedule should be established, decreasing by 250–500 mg daily until discontinued (51). Because the metabolism of valproate is dependent on the cytochrome P450 system, concomitant treatment with drugs that competitively inhibit P450 enzymes, including aspirin, ibuprofen, cimetidine, and erythromycin, must be done cautiously, as they can increase serum valproate levels.

Alpha-2 agonists. Dexmedetomidine, an alpha-2 agonist, has shown benefit in decreasing delirium-associated agitation, both directly by reducing sympathetic outflow from the CNS and indirectly by minimizing utilization of other potentially deliriogenic agents. Clonidine is another alpha-2 agonist, which has less CNS selectivity but can be administered orally in non–critical care settings. There is only limited evidence supporting the role of alpha-2 agonists in adult populations outside the ICU (68), although one randomized controlled trial is under way (71).

As with antipsychotics, a proactive down-titration strategy must be initiated to prevent prolonged administration of these symptom-focused medications beyond the course of delirium or hospitalization and to minimize the risk of rebound hypertension.

Melatonin. As discussed above, there is an emerging literature to support the role of melatonin and melatonin receptor agonists for the prevention of delirium in a variety of hospital settings, yet little is known about the efficacy of melatonin for the treatment of delirium once it has developed. Case studies and retrospective studies indicate that ramelteon is helpful for treating delirium, particularly the hyperactive subtype (72–74). However, generalization of these results is limited by small sample size, lack of randomization, and lack of a control group. Ramelteon was remarkably well tolerated in all these studies, with no significant adverse effects. A double-blind randomized placebo-controlled trial comparing a nightly dose of 3 mg of melatonin to placebo in 56 patients who developed delirium in the setting of organophosphorus compound poisoning showed that the duration of delirium was significantly reduced in the intervention group (6 compared with 3 days; $p=0.001$) (75). In light of the favorable tolerability and safety profile of melatonin in a medically vulnerable population, the role of melatonin and melatonin receptor agonists for the treatment of delirium warrants additional research. In the interim, a low threshold is recommended for an empirical trial of melatonin or a melatonin agonist for sleep consolidation and preservation of the sleep-wake cycle in delirious patients.

Thiamine. Nutritional deficiencies, particularly of the B vitamins, have been associated with delirium. Thiamine (vitamin B_1) deficiency can lead to a spectrum of mental status changes, including Wernicke's encephalopathy (triad of nystagmus, ophthalmoplegia, and mental status changes), Korsakoff's syndrome (irreversible memory impairment, usually as a consequence of untreated Wernicke's encephalopathy), and delirium. Although the most common cause of thiamine deficiency is alcoholism, a variety of conditions that result in malnutrition, including conditions that result in poor feeding, such as anorexia nervosa and orofacial cancers; conditions that limit absorption, such as gastric bypass surgery, gastric cancer, and colon cancer; and hyperemesis gravidarum, can cause thiamine deficiency (76). If thiamine deficiency is suspected, patients should be treated with 250 mg/day of thiamine intravenously for 3 to 5 days (77). Thiamine supplementation should include magnesium repletion, as magnesium is required for the conversion of thiamine into its active form, thiamine pyrophosphate (77).

CONCLUSIONS

The patient in the vignette has many risk factors for delirium, including age, cognitive impairments, multiple medical problems, and male gender. He has physical signs of limited mobility and debilitation, and he is at risk for polypharmacy as well. A psychiatric consultation would include assessment of preadmission neurocognitive baseline and identification of underlying medical etiologies that could contribute to mental status changes (including infection, uremia, and hyperglycemia). Recommendations for intervention would include nonpharmacologic interventions, identification of possible medication-related contributors to delirium, and recommendations for adjunctive medication to manage agitation.

Given the high morbidity and mortality associated with delirium, ongoing efforts to develop and apply proactive interventions to prevent or reduce the severity and duration of delirium are essential. It is crucial to remember that the primary treatment of delirium is identification and management of the underlying medical etiologies, which may be highly variable within and across treatment populations. This adds complexity to research and application of findings across subgroups of populations, even among the geriatric populations who have been the focus of much of the delirium research to date. Safety and symptom relief, including management of the attendant risk of agitation with minimal use of restraints, are important treatment goals. Further research on additional pharmacologic and nonpharmacologic interventions is urgently needed. Meanwhile, we can provide our patients with careful application of the tools currently available to optimize outcomes.

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