

Chapter 4

The Relationship Between Delirium and Mental Health Outcomes: Current Insights and Future Directions



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Learning Objectives

After reading the chapter, individuals will be able to:

- Describe the epidemiology of common psychiatric conditions after critical illness
- Articulate the relationship between delirium and depression and PTSD
- Explain the clinical relevance of an association between delirium and mental health conditions
- Recognize the need for more focused research delirium and psychiatric outcomes

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Introduction

Delirium is a neurological syndrome marked by an acute disturbance of consciousness with inattention and a change in cognition or perceptual disturbance that fluctuates over time. Delirium affects up to 80% of elderly patients and the risk of delirium increases consistently with increased age [1]. Delirium is associated with a wide array of adverse outcomes such as longer hospital lengths of stay, greater length of mechanical ventilation, and increased mortality in the ICU and hospital. Delirium has long been associated with negative consequences even after hospital discharge including discharge to a nursing home, increased risk of death over 2 years, as well as incident dementia [2]. While delirium has consistently been shown to be related to deficits in cognition [3] (with questions persisting related to whether it is simply a marker of injury or fundamentally injurious), less is known regarding the association between delirium and a wide array of mental health difficulties (the three conditions typically studied in ICU survivors are anxiety, depression, and PTSD [post-traumatic stress disorder], not necessarily in that order) [4]. Figure 4.1 describes the overlap of symptoms of PTSD, major depressive disorder (MDD), and delirium. However, early evidence suggests the possibility of linkages of various kinds between delirium and psychiatric phenomena, and this notion

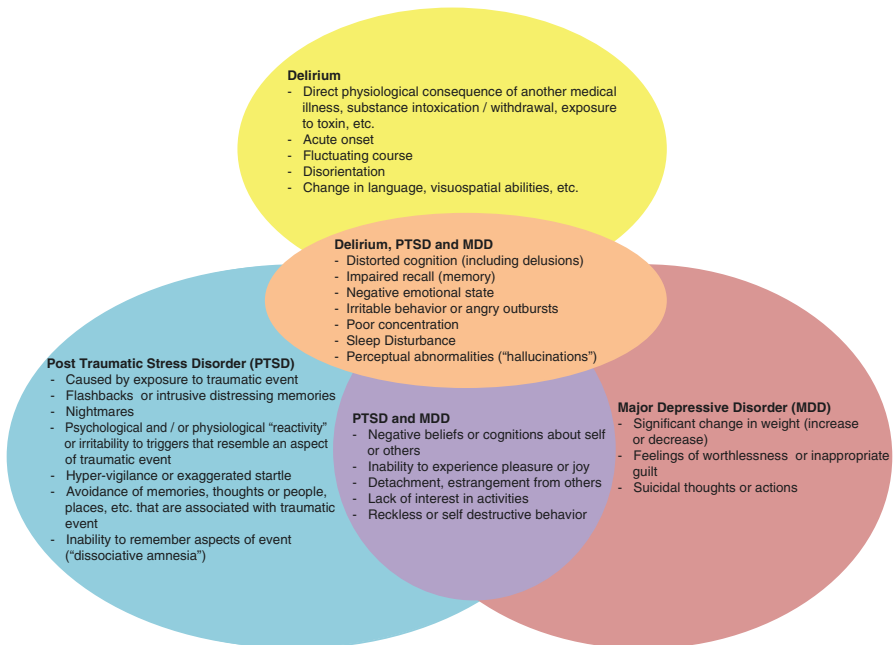


Fig. 4.1 Overlap of signs and symptoms of delirium, post-traumatic stress disorder, and major depressive disorder. During an episode of delirium, patients may experience significant anxiety and mood disturbances, and following an episode of delirium, they remain at an elevated risk to develop symptoms of PTSD or MDD

certainly fits with the experience of seasoned clinicians working with patients following critical illness and other settings in which delirium is a central problem [5]. While a clear imperative exists to treat delirium as a major public health concern, if it is the case that delirium contributes to sequelae of a psychiatric nature, this urgently underscores the importance of finding solutions to prevent and reduce this condition, as doing so may greatly reduce the burden of emotional distress in individuals after the ICU. In the pages that follow, we will describe the epidemiology of common psychiatric conditions in survivors of critical illness, engage issues related to their intersection with delirium, and offer practical solutions for clinicians and recommendations for researchers related to delirium and mental health conditions.

General Anxiety

General anxiety symptoms are exceedingly common among survivors of critical illness, with approximately half of all ICU survivors reporting marked and clinically meaningful symptoms of anxiety up to a year after discharge – a number much higher than the general population’s prevalence [6–7]. Although anxiety is often quite a normal reaction in the context of stress, it can interfere with and impede recovery in multitudinous ways. Symptoms of anxiety during critical illness can have a negative impact on post-ICU psychological functioning and are associated with longer-term PTSD and worse quality of life. While relatively little is known regarding risk factors for ICU-related anxiety, published risk factors to date include demographic and historical variables (e.g., younger age, female gender, premorbid history of anxiety); in-ICU medical and physiological variables (e.g., length of mechanical ventilation, illness severity, sedation management); and environmental variables (e.g., stressful/noisy/chaotic ICU environment) as increasing the likelihood of anxiety [8]. Somewhat surprisingly, no investigations to date have formally explored the relationship between anxiety as a predisposing risk factor for delirium and, alternatively, whether delirium in the ICU is associated with a greater likelihood of anxiety after discharge, perhaps because anxiety, itself, has been studied less than PTSD and depression after critical illness, in particular. As such, we will devote little attention to issues related to delirium and anxiety, focusing instead on issues related to PTSD and depression.

Acute and Post-traumatic Stress

PTSD is a syndrome that develops, by definition, in response to exposure to a trauma or highly stressful event (in this chapter, we will refer to this “trauma” as the experience of critical illness and intensive care treatment). Although it was long characterized as an anxiety disorder, this is no longer the case. Critical illness survivors can develop acute stress symptoms during the course of hospitalization (acute stress

disorder is distinct from PTSD with regard to duration of symptoms) and post-traumatic stress (PTS) symptoms afterward [9, 10]. PTS symptoms are described as symptoms of PTSD without meeting full criteria for PTSD and may include symptoms such as flashbacks, nightmares, unwanted upsetting memories, negative affect, inability to recall key features of the trauma, insomnia, irritability, etc. It has been estimated that at least 20% of ICU survivors experience clinically significant symptoms of PTS during the 1st year after ICU discharge, which is substantially higher than the overall prevalence of these symptoms among individuals in North America and the world [9, 11]. Although these symptoms are often expressed following combat, sexual assault, or a traumatic injury, they also can be a reaction to exposure to critical illness and/or the ICU environment. They may be related to disturbing memories of events that appear “real” to patients but which did not, in fact, actually happen in the way they are recalled (these have been termed “delusional memories”) or, potentially, to delirious states experienced during hospitalization. See below for a more detailed list of risk factors [9, 12]. PTS symptoms after critical illness often include fear of recurrence of the medical condition and/or functional decline that could result in another fear-invoking hospitalization. Avoidant symptoms tend to predominate and manifest as denial of difficulties, apprehension about discussing any signs or symptoms of a possible medical condition with providers, and reluctance to seek help in the first place. Patients often avoid medical appointments and, as a result, may experience greater severity of chronic conditions that have gone untreated.

To meet diagnostic criteria for a formal diagnosis of PTSD, individuals must report complaints across a range of dimensions including intrusion, avoidance, negative changes in cognition or mood, and arousal/avoidance. These symptoms must be present for at least 1 month after exposure to trauma, and they must contribute to some degree of meaningful clinical impairment [13]. As a brief aside, although PTSD is often thought of in “all-or-nothing” terms, symptoms of PTSD fall at points on a spectrum [14]. To be sure, the *Diagnostic and Statistical Manual of Mental Disorders* 5th Edition (DSM-V) provides a very specific definition of PTSD which must be met for individuals to have a formal “PTSD” diagnosis. However, even isolated PTSD symptoms can have a profound impact on individuals and, in some cases, can be disabling.

To provide a clinical example of such cases, one of us (JCJ) worked with a patient many years ago who had classic avoidant features in the absence of other significant symptoms. Mr. Smith (not his real name) had undergone a particularly stressful emergency surgery in which he almost died. In the year after this surgery, he developed a bunion on his foot that made it difficult to walk and was beginning to contribute to problems at his job (which involved walking up to 5 miles a day). After an evaluation with a podiatrist, he was advised that his bunion could be easily removed via a “bunionectomy” – a simple, same-day, office procedure – and that he would quickly be “as good as new.” Despite the probable ease and simplicity of this procedure, he ultimately chose not to undergo surgery due to extreme anxiety about “going under” and to a desire to avoid any situations that might potentially provoke

reminders of his previous experience. Sadly, his pain and problems walking persisted until he eventually lost his job.

Risk Factors for PTSD in ICU Survivors: What About Delirium?

As noted, risk factors for PTSD in ICU survivors have been a source of high interest among both researchers and clinicians, and certain variables such as younger age, female sex, and pre-existing mental health diagnoses appear to consistently confer increased risk of PTSD both in survivors of critical illness and more generally [8]. Memories of frightening psychotic experiences during ICU hospitalization – as we mentioned, these are commonly referred to as “delusional memories” – have been linked with later PTS, though findings in this regard are unequivocal. While perhaps it is the case that most researchers believe delusional memories are particularly likely to form the basis for PTSD in ICU survivors, not all investigations have supported this finding. For example, in an investigation of Swedish ICU patients – 41% of whom reported having delusional memories – no significant associations were observed between delusional memories and anxiety or PTSD [15]. In our clinical experience with ICU survivors, this finding resonates, as some patients seem largely unphased by the presence of bizarre and terrifying “delusional” memories developed in the context of delirium even as others are profoundly traumatized.

As it relates to delirium, the connection between this neurologic syndrome and PTSD is controversial and complicated to unpack. While the notion that delirium – frequently, but not always, described by our patients as deeply disturbing – is a reliable contributor to PTSD seems logical, relatively little *empirical* data support this assertion. Weinert and colleagues, for example, determined that memories of a delirious nature were associated with greater symptoms of PTSD and observed that individuals who were the most alert and awake during critical illness had the lowest risk of PTSD [16]. More generally, however, no clear patterns reflecting specific associations between delirium and PTSD have been found. One recent case series ($N = 2$) of veterans with pre-existing PTSD suggested the possibility that those already suffering from PTSD might be at risk of what is known as “emergence delirium” or “ED” after anesthesia, but this idea, while interesting, has yet to be explored or demonstrated in a larger cohort [17].

Reducing Delirium as a Method of Decreasing PTSD?

To the extent that delirium and delusional memories are possible contributors to PTSD, it appears reasonable to consider carefully exploring sedation strategies as a target for intervention. This has been done in the context of ICU care recently, as

certain approaches to sedation and pain management, for example, are widely known to be deliriogenic. In particular, researchers have focused on the role of benzodiazepines such as midazolam and lorazepam as well as opiates, as all of these have been found in at least some studies to be potentially related to post-ICU PTSD [18]. While the thoughtful use and reduction of medications of various kinds in the ICU should be heralded as progress, and while a clear “sea change” has occurred in recent years (resulting in patients being more active and alert and probably less delirious as a result), the impact of this paradigm shift on PTSD is unclear. Regardless, the other benefits of sedation reduction are substantial despite the mental effects of such an approach being unclear. Data from several sources indicates that factual memories of ICU-related experiences – presumably more likely to occur within the context of sedation – may be protective against future psychiatric distress [19–20]. Lighter sedation may in fact be protective of neuropsychiatric disorders after discharge, and amnesia of the ICU stay has been associated with increased neurocognitive sequelae [21, 22]. Briefly, the notion here is that factual memories of medical or ICU-related events – even if quite upsetting – have the effect of grounding patients in “reality” which may be preferable to the presence of psychotic or delusional memories.

Depression

Depression and depressive symptoms also are prevalent in the context of critical illness and ICU hospitalization. It appears that the point prevalence of clinically significant depressive symptoms may be as high as 30% after discharge, much higher than the US population’s 7% for major depressive disorder or 10% for any mood disorder (which includes major depressive disorder, dysthymia, and bipolar I and II) [23]. Depression includes cognitive-affective and somatic symptoms (believed to be particularly prominent in the context of critical illness), and it has been posited that cognitive-affective symptoms in particular (feelings of hopelessness, affective symptoms, etc.) may underlie the relationship between depression and chronic diseases through mechanisms which may include dysregulated cortisol and nonadherence to medical regimens [24]. Alternatively, in survivors of medical and surgical critical illness, somatic symptoms that largely involve such things as fatigue, problems sleeping, deficits in initiation, etc. appear to be primary [25]. In general, symptoms of depression may increase vulnerability to critical illness as individuals with significant symptoms of depression may be likely to succumb to unhelpful health-related behaviors such as smoking, inactivity, excessive alcohol use, poor dietary choices, and non-compliance with recommended treatment regimens [26]. It appears that patients with serious depression tend to die up to a decade earlier than their non-depressed counterparts, often from chronic health conditions such as cardiac disease, chronic obstructive pulmonary disease (COPD), and diabetes, among many others [27–28].

Exploring the Association Between Delirium and Depression

Nearly 30 studies have explored the complex relationship between depression and delirium, with most of them evaluating depression as a risk factor for delirium and a few of them focusing on whether delirium drives the development of depression [29–32]. In general, it appears that depression reliably heightens the likelihood of experiencing delirium, and this finding is generally consistent across a wide array of patient populations, including those with critical illness. While the strength of the relationship between depression and delirium varies, the increased risk of delirium in individuals with depression is often very high [29–30]. Less is known about whether delirium contributes to poorer psychiatric outcomes, perhaps because most researchers have focused on the cognitive sequelae of delirium to the exclusion of a focus on psychiatric outcomes (not surprising, as delirium is widely conceived of as a neurologic and not a psychiatric condition) [33]. Despite the widely varying methodology and rigor of the studies in question, a majority have identified an association between delirium and subsequent depression, reflected in outcomes such as higher scores on depression measures at distal timepoints [34].

Common Processes Underlying Delirium and Depression

As depression is the primary psychiatric condition to be associated with delirium, we will briefly unpack issues related to physiology that may potentially undergird both of these conditions, recognizing that few if any investigations have explored these relationships as such. While questions exist regarding the mechanisms that contribute to the development of delirium, one of the most prominent theories involves imbalances in dopaminergic and cholinergic pathways as well as disruptions pertaining to inflammation [34]. Importantly, these are the same mechanisms widely implicated in the emergence and maintenance of depression, along, perhaps, with altered cytokine expression, itself, a major risk factor for depression. Also fundamental to both delirium and depression are various pathologies related to sleep, reflecting potential issues in circadian regulation [35].

Treatment of Delirium and Depression

If it is the case that delirium and depression potentially are influenced by common mechanisms, this insight may have practical pharmacologic implications. One key implication, certainly, involves exploration of whether the mood-related difficulties potentially present in delirium are simply reflective of this neurologic syndrome or whether, alternatively, they are reflective of an actual disorder of mood [36]. If depression is indeed present, then treatment should likely avoid agents with

prominent anticholinergic properties as there is some evidence that these may be deliriogenic [37–38]. Yet another clinical insight pertains, as we've discussed, to the centrality of circadian rhythm disruption in those with both delirium and depression. It may be that sleep-related interventions, among them melatonin, might be effective in the management of both these conditions, although evidence for the effectiveness of melatonin in delirium is extremely preliminary [39, 40]. Finally, if it is the case that depression is a major risk factor for the development of delirium, the integration of mental health strategies in the ICU in an effort to prevent the development of delirium may be crucial as a reduction in incident depression may translate into a reduction in incident delirium.

A Research Agenda Related to Delirium and Mental Health

Individuals who have been hospitalized in the ICU and experience delirium tend to experience longer hospital duration and higher mortality rates than those who did not experience delirium. There are many risk factors for development of delirium including genetic (e.g., APOE-4 allele), pathophysiological (e.g., infection), medical (e.g., sedating medications), environmental (e.g., chaotic ICU environment, dysregulation of sleep/wake cycle), or mental health (e.g., depression). A prior history of depressive symptoms and depressive disorders is common among individuals who experience delirium, and depression also is a common consequence of delirium. The exact mechanisms by which delirium and mental health are correlated in a bi-directional manner following critical illness remain largely unknown. There can be noted disruptions to cognition during both delirium and depressive episodes. Throughout the extant literature, there is indication of a similar pathophysiological pathway for development of both depression and delirium, a pathway involving stress and inflammatory responses as well as monoaminergic and melatonergic functions. Exposure to various medications also has been associated with onset and duration of delirium (e.g., benzodiazepine and opioid medications) as well as environmental culprits such as physical restraint or immobilization.

Among all the various psychological, behavioral, and environmental interventions thought to prevent delirium, early mobilization (e.g., ambulation, exercise, and range of motion implemented within the first days of ICU hospitalization) may be key. Mobilization, or physical activity, also has been associated with prevention of a depressive episode as well as enhanced management of depressive symptoms, regardless of any other intervention employed (e.g., psychotherapy or antidepressant medication). All of this evidence for a common etiology and common pathophysiological pathway highlights the promising possibility for common modes of prevention and intervention. At this point, however, the field of critical care psychology lacks animal models and basic science research that can further enhance our understanding of the pathophysiological mechanisms, as well as the intersection between delirium and mental health outcomes. As a field, we also are lacking studies designed to enhance our understanding of the various phenotypes of delirium

that may present and how those phenotypes may be associated with a mental health history or mental health outcomes. We also are desperately in need of better tools of assessment – both for delirium and depressive symptoms/depressive disorders – for enhanced sensitivity and specificity of diagnosis to guide treatment efforts.

Conclusions

Delirium continues to be pervasive in critically ill populations and in medical and geriatric populations more generally. While commonly linked to cognitive problems, this neurologic syndrome is also associated with mental health difficulties and, more specifically, with depression. Evidence of an association between delirium and PTSD is so far inconsistent. Indeed, the presence of delirium increases vulnerability to the development of mental health-related difficulties. Interventions to decrease delirium in a variety of populations may in turn prevent the emergence of incident depression or even PTSD, but this remains a question in need of future study. Although little attention continues to be paid to the dynamic interplay between delirium and psychiatric conditions, clinicians and patients should be aware of the relevance of delirium not only to outcomes such as mortality, hospital length of stay, and cognition but also to conditions such as depression.

Take-Home Messages

- The nature of the association between delirium and mental health difficulties has been relatively little studied and remains somewhat unclear.
- While research on the link between delirium and PTSD has been somewhat contradictory, evidence consistently supports a relationship between delirium and depression, and this relationship exists in both directions.
- Interventions that reduce delirium may also decrease the incidence of prevalence of ICU-associated psychiatric syndromes, although this requires further study.
- Dedicated research programs – marked by increasingly sophisticated multidisciplinary approaches – should continue to elucidate the fundamental underpinnings of the relationships between delirium, anxiety, depression, and PTSD.

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