

June 26, 2021

Centers for Medicare and Medicaid Services
Department of Health and Human Services
Hubert H. Humphrey Building, Room 445-G
200 Independence Avenue, SW
Washington, DC 20201

Dear Centers for Medicare and Medicaid Services (CMS),

We write respectfully regarding the complexity designation of *delirium due to a known physiological condition* (F05) in the DRG classification system, where it is currently identified as a complication or comorbidity (CC). We request that this diagnostic code be designated as a major complication or comorbidity (MCC) as this would recognize the importance of delirium in determining illness severity and complexity in the hospitalized patient. This change would also bring *delirium due to a known physiological condition* into alignment with *metabolic encephalopathy* (G93.41), which is currently recognized as an MCC.

The term delirium is either used synonymously with acute encephalopathy (hereafter, referred to simply as encephalopathy) or, in the most reductionist definition of delirium, considered an agitated or hyperactive subtype of encephalopathy (Oldham MA & Holloway RG, 2020). In this proposal, we make a case for this change by comparing the definitions of encephalopathy and delirium. We also provide an empirical argument by outlining the scientific evidence of the dire effects that delirium has on the patient's clinical course. Whether considered a severe subtype of encephalopathy or synonymous with encephalopathy, delirium has the potential to cause significant adverse outcomes in hospitalized patients suffering from this complex and dangerous disorder.

The National Institute of Neurologic Disorders and Stroke (NINDS) defines encephalopathy as a descriptive term utilized for any diffuse disease that alters brain function or structure. They explain that the hallmark of encephalopathy is an altered mental state that may cause a progressive loss of memory and cognitive ability, subtle personality changes, inability to concentrate, and alteration of consciousness (<https://www.ninds.nih.gov/Disorders/All-Disorders/Encephalopathy-Information-Page>). NINDS states that encephalopathy may be caused by infectious agents, metabolic disturbances, exposure to toxic elements or medications, poor nutrition, or lack of oxygen or blood flow to the brain.

The definition of delirium is essentially equivalent to that of encephalopathy. Delirium describes an impairment in brain function leading to an acute alteration in mental status due to an underlying toxic, metabolic, or neurologic insult. The signs and symptoms of delirium include an acute disturbance in attention and awareness, change in cognition, altered level arousal, and typically a fluctuating clinical course. Clinicians and researchers have used many terms to describe delirium historically, such as toxic/metabolic encephalopathy, intensive care unit (ICU) psychosis, acute confusion, and acute brain failure. It was not until 1987 that the American Psychiatric Association (APA) provided diagnostic criteria for delirium with the publication of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (APA 1987). The criteria have been further refined with subsequent editions of the DSM leading up to the current



DSM-5 (APA 2013), which specifies that delirium is a “direct physiological consequence” of a medical condition, substance intoxication or withdrawal, toxin exposure, or multiple etiologies. The DSM criteria have become the most widely accepted clinical and research standards to diagnose patients suffering from delirium. The features of delirium have also been operationalized in the International Classification of Diseases version 10 (ICD-10) (World Health Organization, 1992). The core similarities between the NINDS and DSM definitions of delirium are outlined in table 1.

Table 1: Characteristics of delirium and encephalopathy

	Delirium	Encephalopathy
<i>Altered mental state</i>	X	X
<i>Cognitive impairment</i>	X	X
<i>Impaired attention</i>	X	X
<i>Altered level of arousal</i>	X	X

A recent position statement on the preferred nomenclature of delirium and encephalopathy, endorsed by 10 medical societies, further clarified the integral relationship between these two clinical entities (Slooter AJC, et al. 2019). The statement defines acute encephalopathy as “a rapidly developing (in less than 4 weeks) pathobiological brain process which is expressed clinically as either subsyndromal delirium [*n.b.*, meeting some but not all delirium criteria], delirium or coma.” Delirium, with its defined clinical phenotype, provides empirical evidence of an underlying encephalopathy, and a DSM-5 diagnosis of delirium not only implies but incorporates the encephalopathy itself. In other words, a diagnosis of *delirium due to a known physiological condition* is a diagnosis of *metabolic encephalopathy* with the added specification of a threshold of clinical severity based on the mental status.

The consensus in the diagnostic criteria of delirium provided by the DSM has allowed standardization of research along with greater comparability between studies exploring the short and long-term consequences of delirium on hospitalized patients. This is in stark contrast to encephalopathy, which lacks well-referenced research criteria. In addition, there are no defined treatment pathways for metabolic encephalopathy. In stark contrast, modern clinical treatment guidelines are available for delirium in the United States (e.g., by the American Geriatrics Society and the Society for Critical Care Medicine) and internationally (e.g., the National Institute for Health and Clinical Excellence, the Scottish Intercollegiate Guidelines Network, European Society of Anaesthesiology, Association of Scientific Medical Societies of Germany, and Japanese Psycho-Oncology Society and Japanese Association of Supportive Care in Cancer).

Delirium is linked to increased mortality across multiple patient populations. Patients who develop delirium in the ICU have a two-to-four-times increased risk of death when compared to a matched patient population who do not develop delirium (Ely EW, et al. 2004). Patients who experience delirium on a general medicine unit have one-and-a-half times the increased risk for death in the year following hospitalization (Leslie DL, et al. 2005). Delirious patients in the emergency department have an approximately 70% increased risk of death during the first six months following the visit (Han JH, et al. 2010).

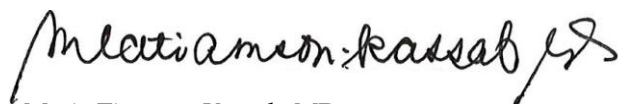
An increase in mortality is not the only adverse outcome suffered by patients experiencing delirium. Delirium has been associated with an impairment in physical function for 30 days or more after discharge (Rudolph JL,

et al. 2010; Oldenbeuving, AW, et al. 2011). Delirium has also been linked to new cognitive impairment in previously healthy individuals a year after their ICU admission and the occurrence of delirium (Pandharipande PP, et al. 2013). The further cognitive impairment was significant, with over 30% showing deficits similar to patients with a mild traumatic brain injury. In patients with prior cognitive impairment, such as Alzheimer's disease, the pre-existing dementia is worsened by an episode of delirium (Fong TG, et al. 2009). In the critically ill patient, delirium is associated with more medical complications, longer duration of mechanical ventilation, higher rates of discharge to skilled nursing facilities, and longer length of stay in ICU and hospital when compared to critically ill patients who were not delirious (Zhang Z, et al. 2013).

The diagnostic terms delirium and encephalopathy are often used interchangeably, and this is because they refer to a shared set of acute neurocognitive conditions. They both describe core symptoms of impairment of level of consciousness and cognitive change caused by a medical condition or substance. However, unlike encephalopathy, delirium has well-validated diagnostic criteria that have allowed for the characterization of its complexity and numerous adverse outcomes. The adverse outcomes of delirium are severe. Indeed, the robust literature detailing the impact of delirium on patient and caregiver distress, care complexity and costs, readmissions, rates of functional decline, institutionalization, cognitive decline, subsequent dementia diagnosis, and mortality simply has no parallel in the encephalopathy literature.

Therefore, we request that CMS consider designating *delirium due to a known physiological condition* as MCC so that it is appropriately on par with *metabolic encephalopathy*. We firmly believe and submit that this specified diagnosis of delirium meets the MCC-qualifying threshold of clinical severity and complexity and deserves recognition as such.

Sincerely,



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