

## REVIEW

# Psychopathology after admission to the intensive care unit

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## Abstract

A substantial number of patients who have been admitted to an intensive care unit (ICU) face both physical, cognitive and mental impairment related to their critical illness up to years after discharge. Up to half of the patients undergoing a prolonged ICU admission report symptoms of psychopathology afterwards, which hampers their full recovery. Complaints often include an affective component: symptoms of anxiety, depression, and post-traumatic stress disorder are common. The development of psychopathology is multifactorial and depends on patient characteristics (e.g., female sex, history of psychiatric disease), and ICU-related factors (e.g., time on the mechanical ventilator, administration of sedatives), and hypothalamic-pituitary-adrenal axis dysfunction. Some preventive and therapeutic interventions are available and a timely and multidisciplinary approach may help to reduce psychopathology after ICU admission.

## Introduction

In the past decade, it has become clear that admission to an ICU can act as a trigger for long term physical and mental morbidity. With over 70,000 patients admitted to ICUs in The Netherlands yearly, it is important to obtain an overview of these adverse effects and address potential preventative and treatment strategies.

## Post intensive care syndrome

ICU treatment aims at patient survival of critical illness, and establishes the foundation for rehabilitation and recovery of quality of life. Not every patient, however, makes a complete recovery after ICU survival.<sup>[1-4]</sup> Physical symptoms, such as muscle weakness, dysphagia, and chronic pain, but also cognitive impairment and mental health problems are commonly reported after ICU admission. Under the denominator 'post intensive care syndrome' (PICS), the activities of daily living and health-

related quality of life of ICU survivors can be affected. Recovery might be hampered up to years after discharge.<sup>[5,6]</sup> The ongoing improvement of ICU care and a corresponding decrease in ICU mortality may lead to a growing patient population at risk for long-term impairment of daily life. Critical illness and intensive care treatment may also have an impact on the patients' family members as they may also suffer from psychopathological symptoms.<sup>[7-9]</sup>

## The ICU and psychopathology

Patients often perceive their ICU admission as very stressful, and in light of the mental aspects of PICS, half of the patients report symptoms of anxiety, depression or post-traumatic stress disorder (PTSD) after discharge.<sup>[10-13]</sup> These symptoms may occur up to years after ICU discharge, and factors that might influence the course of these long-term consequences are receiving growing attention.<sup>[14,15]</sup>

Anxiety can manifest as excessive worrying about a variety of topics, events or activities. This excessive worrying is characterised by the absence of a specific threat or in a manner that is disproportionate to the actual risk. Furthermore, the worry may be accompanied by reassurance seeking from others and is experienced as very challenging to control. The latter can cause edginess, fatigue and difficulty to concentrate.<sup>[12]</sup>

Depression is characterised by a depressed mood and/or loss of interest or pleasure in activities that were normally enjoyed. Of the following symptoms, at least four should be present for the past two weeks or longer (for major depression diagnosis): sleep disturbances, fatigue or loss of energy, weight or appetite changes, psychomotor agitation or retardation, feelings of worthlessness or guilt, and recurrent thoughts of death or suicide.<sup>[12]</sup>

PTSD can occur after exposure to a stressful or traumatic event, and is diagnosed by evaluation of the presence of several criteria. Patients with PTSD have been confronted by actual or

threatened death or serious injury, or by a threat to the physical integrity of self or others, involving intense fear or helplessness in the person's response. This experience can lead to recurrent and intrusive recollections of the event (e.g. involuntary and upsetting memories or flashbacks), which causes psychological distress and physiological reactivity. Patients often persistently avoid stimuli associated with the event, and can estrange from others caused by a restricted range of affect. The presence of increased arousal, combined with the symptoms previously mentioned for at least four weeks causes significant impairment in their social and occupational functioning.<sup>[12,16]</sup>

Former ICU patients can suffer from different affective symptoms over the course of time after discharge. Symptoms often co-occur as well, since anxiety, depression, and PTSD are all frequently preceded by some form of stress.<sup>[12]</sup> More specifically, the combination of sensory deprivation on the one hand (i.e., with regard to enjoyable or interactive stimuli), and sensory overload (i.e., comprising monotonous noises and invasive procedures) on the other hand is exceptionally stressful.<sup>[17]</sup> Although not all patients who undergo ICU treatment develop psychopathology, the described prevalence is relatively high. It remains largely unknown which patients are most at risk for developing psychopathology. Several potential risk factors have been identified. Some are patient related (e.g. episodes of psychiatric morbidity in their medical history, sex, exposure to trauma before admission to the ICU); others are ICU dependent (e.g. length of ICU stay, use of mechanical ventilation, use of psychoactive medication during the admission).<sup>[14]</sup> Symptoms of anxiety and depression are reported in 24% and 16% of patients respectively;<sup>[16]</sup> PTSD can occur in up to 44% of former ICU patients.<sup>[17]</sup> Although these percentages are predominantly based on studies with patient questionnaires instead of interviews with patients, they suggest a high prevalence of potentially clinically relevant psychopathology symptoms after ICU admission.

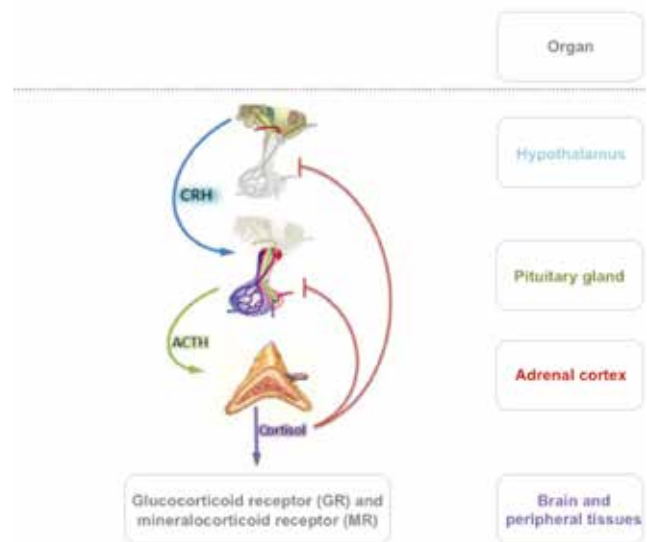
### Vulnerability to psychopathology

Whether someone is prone to develop symptoms of anxiety, depression or PTSD after ICU admission depends on several factors. Patient-related factors include female sex and older age. Psychological risk factors include stress, experienced fear and frightening memories related to the ICU admission and a lifetime history of any psychiatric disorder.<sup>[13,18-21]</sup> Clinical factors that have been identified are duration of sedation, mechanical ventilation, and length of hospital stay.<sup>[20]</sup>

Especially psychoactive medications, such as benzodiazepines and anticholinergic drugs, are noteworthy. Benzodiazepines are suspected to negatively affect neuropsychiatric outcomes, both during and after ICU admission.<sup>[22,23]</sup> Although recent guidelines opt for restrictive administration, these drugs are still commonly used. With regard to anticholinergic drugs, cholinergic deficiency has not been specifically linked to delirium during ICU admission. Nevertheless, preclinical research accredits the regulation of

stress resilience, and anxiety- and depression-like behaviour to cholinergic signalling.<sup>[24]</sup> In frail elderly patients, more depression and anxiety is reported when they are subjected to a higher anticholinergic load; since the average age of ICU patients is over 65, these results could well be representative for the critically ill.<sup>[25]</sup> In general, neuropsychiatric effects of medication administered in the ICU could influence psychopathology development, not only limited to the duration of ICU stay, but also thereafter.

The hypothalamic-pituitary-adrenal (HPA) axis plays a pivotal role in the adaptation of individuals to changing environment.<sup>[26,27]</sup> Consequently, impaired functionality of the HPA axis is thought to contribute to the development of symptoms of anxiety, depression and PTSD. Exposure to stress rapidly stimulates the secretion of the end product of the HPA axis: glucocorticoids (*figure 1*).<sup>[27]</sup> This activates the 'fight or flight' response, and subsequent termination involves binding of glucocorticoids (i.e., cortisol) at the glucocorticoid receptor and mineralocorticoid receptor in the brain. Besides the naturally released glucocorticoids, synthetic glucocorticoids such as prednisolone and dexamethasone are able to bind these receptors. In the ICU setting, synthetic glucocorticoids are sometimes administered to attenuate the inflammatory response and reduce the risk of major adverse events in specific cases.<sup>[28-31]</sup> This could affect HPA axis functionality.



**Figure 1.** Schematic overview of the hypothalamic-pituitary-adrenal (HPA) axis

The figure depicts the physiological and hierarchical pathway to cortisol secretion from the adrenal cortex. It includes the negative feed-back loop (modified from Eckstein et al. 2014).<sup>[47]</sup>

CRH = corticotrophin-releasing hormone; ACTH = adrenocorticotropic hormone

Potential prevention measures for ICU-related psychopathology Successful implementation of treatment measures requires a multifactorial and interdisciplinary approach. If possible, an

image of the patient's psychiatric history should be formed during the ICU admission to assess the likelihood of recurrent psychopathology after discharge. Contacting the patient's general practitioner and/or asking relatives (if possible), could provide valuable information. Furthermore, awareness of the ICU as a stressful environment is essential. Many measures are necessary for survival and optimal treatment of critical illness. Therefore, coping with these various stressors is key to minimising their contribution to the occurrence of psychopathology. One of the interventions that showed most effectiveness with regard to prevention of PTSD after discharge is the ICU diary.<sup>[32]</sup> In this diary, relatives and/or ICU caregivers keep a record of daily events. It is a low cost and highly acceptable tool, which helps the patient understand what happened during their ICU admission. It is obvious that ICU patients need well-titrated sedation and analgesia, and ample reassurance from their caregivers, especially when undergoing unpleasant procedures. However, administration of too little or too many analgesics and/or sedatives can be harmful. Especially excess sedation has been proven to prolong the duration of mechanical ventilation, ICU and hospital length of stay, and lead to higher mortality rates and accrued expenses.<sup>[33]</sup> Recent guidelines offer clear points of action, which allow adjustment of analgesia and sedation to meet the requirements of each individual ICU patient.<sup>[33,34]</sup> Wake up calls and spontaneous breathing trials decrease the time on mechanical ventilation and the usage of sedatives, and are associated with a better – psychopathological – outcome.<sup>[35]</sup> Next to daily evaluation of the level of sedation, and the use of standardised scoring tools, the foundation of these protocols has changed over time. In contrast to the classic approach, which primarily involved a sedative and addition of analgesics, up to date protocols are based on establishing adequate analgesia first and only supplementing hypnotics if necessary. The latter results in a significant reduction in the use of sedatives, which is beneficial for patient outcome, including the occurrence of long-term psychopathology.<sup>[36,37]</sup> If additional sedation is necessary, the drug of choice matters. A break in trend is also notable in this field: traditional benzodiazepines have been compared with the more recently available  $\alpha$ -2 adrenoceptor agonists (e.g., clonidine and dexmedetomidine). Patients not receiving benzodiazepines showed a reduction in the duration of mechanical ventilation and ICU length of stay. Although the quality of evidence was low, usage of dexmedetomidine did not increase the risk of delirium, nor mortality.<sup>[36-39]</sup>

A Cochrane review identified corticosteroids given during or shortly after a stressful event, as a powerful intervention to reduce the risk of PTSD.<sup>[40]</sup> Within the ICU setting, however, we believe that there is at present insufficient evidence for administering corticosteroids for preventing PTSD.

### Treatment perspectives

Patients can be tracked after ICU discharge to assess symptoms

of ICU-related psychopathology. Knowledge and expertise of ICU caregivers can provide valuable insights to optimise aftercare and contribute to recovery. There are established treatments for depression, anxiety and PTSD. By identifying who is most at risk to develop long-term psychopathology, it might be possible to estimate receptivity to intervention strategies. Hence, their effectiveness is likely to depend on who is prone to exert an inadequate adaptive stress response, and who will show resilience. This fits the aspired concept of personalised medicine and could contribute to healthcare efficacy; it promotes the best quality of care for patients admitted to an ICU.

A truthful recall and realistic memory formation contribute to recovery and are essential cornerstones of coping with symptoms of stress-related psychopathology. Informing former ICU patients about the course of their ICU stay and helping them to distinguish between delusional experiences and real events facilitates their recovery. Developments in this field of psychoeducational interventions which benefit coping strategies are ongoing. An upcoming technique for the treatment of PTSD is eye movement desensitisation and reprocessing (EMDR). This technique involves the recall of traumatic experiences while a trained therapist applies diverging stimuli (e.g. sounds administered by headphones or inducing eye movements) which activate novel memory formation.

<sup>[41,42]</sup> Although it is predominantly applied in patients who are suffering from trauma-associated symptoms (i.e., PTSD), EMDR therapy could still be useful in patients with symptoms of anxiety or depression to improve affective symptoms. Nevertheless, the therapeutic efficacy of EMDR beyond PTSD is still the subject of debate, and more research comparing the therapeutic value of EMDR with standard practice (e.g., cognitive behavioural therapy) is needed. One of the most innovative developments in this field is the use of virtual reality. It is applicable in different ways, either serving renewed recollection of memory or to achieve relaxation. It can also be used in the pre-ICU setting to help prepare patients for their ICU admission, and it can be used for training purposes.<sup>[43-46]</sup>

Although PICS is receiving more and more attention, the current healthcare system still does not meet the needs of many patients who have been admitted to the ICU. The way in which ICU aftercare is organised varies between hospitals. Best practices are yet to be determined.<sup>[15]</sup> The Society of Critical Care Medicine founded the THRIVE collaboration to share expertise about ICU aftercare, and defined key topics that should be considered when preparing patients for discharge. These involve equipment needed for daily activities at home, medications, follow-up appointments and educating patients and their families about recovery after critical illness. The ultimate goal of the THRIVE collaboration is to identify the best interventions for patients with PICS, in order to decrease readmission rates and morbidity and improve health-related quality of life. At this moment, a new study is being prepared at the University Medical Center of Utrecht, the Netherlands, to evaluate the effect of extensive rehabilitation and aftercare on PICS at six months after ICU admission.

## Conclusion

In conclusion, several ICU- and patient-related risk factors influence the occurrence of stress-related psychopathology after ICU admission. Symptoms of anxiety, depression and PTSD after ICU admission can be relieved if these risk factors are comprehensively managed. Identifying patients at risk on the one hand, and application of preventive and treatment interventions on the other hand, are key.

## Conflict of interest

All authors declare no conflicts of interest. No funding or financial support was received.

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