

## Commentary

# Medical post-traumatic stress disorder: catching up with the cutting edge in stress research

Craig Weinert<sup>1</sup> and William Meller<sup>2</sup>

<sup>1</sup>Pulmonary, Allergy and Critical Care Medicine, University of Minnesota Medical School, 420 Delaware St SE, Minneapolis MN 55455, USA

<sup>2</sup>Department of Psychiatry, University of Minnesota Medical School, 420 Delaware St SE, Minneapolis MN 55455, USA

Corresponding author: Craig Weinert, [weine006@umn.edu](mailto:weine006@umn.edu)

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See related research by Boer *et al.*, <http://ccforum.com/content/11/1/R30>, related research by Jackson *et al.*, <http://ccforum.com/content/11/1/R27>, and related research by Girard *et al.*, <http://ccforum.com/content/11/1/R28>

## Abstract

We briefly summarize two original research papers and a review article. We then review the formal structure of the diagnosis of post-traumatic stress disorder (PTSD) and discuss the use of continuous measures of PTSD in comparison with diagnostic instruments. Problems with distinguishing incident from prevalent PTSD cases lead to questions of whether medical PTSD is a new important problem. By examining current studies, we demonstrate that medical PTSD is lagging in fundamental and interventional research but we discuss how medical PTSD has unique opportunities to develop causal models that could inform the greater field of stress studies. We conclude by advocating that future medical PTSD research efforts should focus on understanding how fundamental brain processes are affected during acute medical stress.

In this issue of *Critical Care*, two new observational studies of post-hospitalization post-traumatic stress disorder (PTSD) [1,2] are presented, as well as a review of 16 studies of non-injury-related critical illness PTSD [3]. The major finding of the paper by Boer and colleagues [1] was that in a cross-sectional study of patients that were surgically treated for secondary peritonitis (not trauma-related), patients that had to be treated in an intensive care unit (ICU) had fourfold greater odds of having significant levels of PTSD symptomatology (Post-Traumatic Symptom Scale (PTSS)-10  $\geq$  35) at long-term follow-up in comparison with patients not requiring ICU care, after controlling for age, gender, and initial severity of illness. Identifying 'ICU care' as an independent predictor of PTSD suggests that there are element(s) of ICU care or pathophysiologies that are on the causal pathway to PTSD. Girard and colleagues [3], in a small study with a single follow-up time point of 6 months (albeit with a rate of loss to follow-up of 48%), found that total lorazepam dose was associated with PTSD severity, but delirium or initial

severity of illness was not. Girard and colleagues are appropriately cautious in ascribing cause and effect to the association with lorazepam because sedation therapy was not randomly assigned. In addition, it is hard to reconcile these findings with previous reports from the same cohort that showed an association between lorazepam and delirium [4]. In their review article, Jackson and colleagues [2] show that small sample sizes, problems with case definition and substantial rates of loss to follow-up make current estimates of post-ICU PTSD prevalence unreliable and impair the development of causal models for PTSD in medical patients.

These papers raise several issues that are worth comment. First, what is the controversy about the widespread use of 'screening' instruments rather than 'diagnostic' PTSD instruments or interviews? In the formal definition of PTSD in DSM-IV [5], this disorder is diagnosed when there are a minimum number of symptoms distributed across all three symptom clusters of intrusive recall, avoidance/emotional numbing and hyperarousal. Other criteria, such that the symptoms should cause distress or impairment of function (broadly defined), are required for PTSD and almost all psychiatric diagnoses. Having many symptoms in one or two clusters but not in others is insufficient for a DSM diagnosis. It is also likely that the clusters are not equal in contributing to a global diagnosis of PTSD: symptoms in the 'avoidance/numbing "C"' cluster are more predictive of a pervasive disturbance than recall and hyperarousal symptoms [6].

Continuous measures such as the PTSS-10 combine frequency ratings (1 to 7, from never to always) in 10 symptoms. It is possible that a patient with a rating of 7 for five symptoms would have an aggregate score above the threshold value of 35, even though their symptoms were not

ICU = intensive care unit; PTSD = post-traumatic stress disorder; PTSS = Post-Traumatic Symptom Scale.

distributed across all the symptom clusters. However, overdiagnosis by the PTSS-10 does not seem to be a problem – at least in patients with acute respiratory distress syndrome who were examined years after mechanical ventilation, in which the PTSS-10 had a specificity of 98% and 77% sensitivity [7]. Even if all post-ICU patients (PTSD prevalence of about 15%) were screened, the positive predictive value would still be high at 87%. Certainly, continuous measures are more suitable for regression modeling, which was done in both papers, but interpretation may be more difficult than other continuous variables. For instance, it is accepted that an age of 35 years represents the same quality as an age of 70 years, just less of it. It is less clear that a PTSS-10 score of 20 represents the same quality as a score of 40, just half as much. Like many other design features, researchers have to make trade-offs between ease of data collection, improved statistical power, and interpretability of the results.

A second issue complicating PTSD research is how to distinguish incident from prevalent cases. Schelling and colleagues [8] found that 25% of PTSS-10 positive cases 6 months after cardiac surgery had had scores of 35 or more *before* surgery. If one considers that many medical ICU patients are chronically ill and have been hospitalized or mechanically ventilated previously, it is easy to understand the difficulty in interpreting epidemiology studies if a 'baseline' assessment cannot be performed.

Reviewing the citation dates from the accompanying articles, a reader might guess that 'medical PTSD' is a new disease. But is it really a previously under-recognized condition, as sleep disordered breathing was 20 years ago, or is it 'medicalization' of human suffering and distress whereby clinicians confuse suffering with psychopathology? How much can we transform an already amorphous psychiatric syndrome (and its accompanying measurement tools) to 'fit' the distinctive characteristics of recent ICU survivors and still call it by the same name? An ambitious research agenda might be to develop a taxonomy to recategorize the gamut of distressing psychological symptoms prevalent in recent ICU survivors beyond the labels of 'depression', 'PTSD', or 'anxiety'.

What is clear, however, is that in the traditional disease research pathway (from incidence/prevalence epidemiology and natural history to risk factor discovery and pathogenesis to prevention and treatment strategies), medical PTSD research, with few exceptions [9], is mostly at step 1 or 2. For instance, using the search phrase 'PTSD' we queried the US National Institutes of Health currently funded grants database [10] and found 115 research projects. Only six of these were investigating 'medical' PTSD, and these projects all involved patients in the ambulatory settings exposed to the 'stress' of receiving a potentially life-threatening diagnosis such as colorectal cancer or infection with HIV. Readers of *Critical Care* may be surprised that the bulk of NIH-supported PTSD

**Table 1**

**Clinical trials registered at <http://clinicaltrials.gov> investigating PTSD treatments**

- Non-medication therapies: eye movement desensitization, yoga, cognitive behavioral therapy, brief eclectic psychotherapy, brief psychological intervention, mantra repetition
- Medication therapies: sertraline, mirtazapine, quetiapine, ziprasidone, risperidone, NK1 antagonist, levetiracetam, prednisone, cortisone, prazosin, propranolol, cycloserine, divalproex
- Other physical-based therapies: transcranial magnetic stimulation, virtual reality, acupuncture

research starts a long way outside the traditional medical model to include long-term social pathology and public health issues such as intimate partner violence, childhood neglect, sexual abuse, and refugee health. Veterans' and other national agencies may support a different mixture of PTSD studies. We also found 22 ongoing registered PTSD clinical trials [11] (see Table 1) that demonstrate the enormous range of treatments under investigation – none of the studies are in post-ICU patients. Only three of the trials listed in Table 1 are designed to prevent PTSD; all others are to treat established cases.

Although medical PTSD research lags behind other areas, we believe that critical care investigators are in a unique position to contribute to the greater field of stress studies. Unlike subjects exposed to the stressors of combat, childhood neglect or physical assault who almost always present for treatment after the stressor is over, during critical illness we can characterize the stressor or intervene while the stressor is occurring. By relating severity of illness (but more than a simple day-1 Acute Physiology and Chronic Health Evaluation (APACHE) II score), medications, cortisol or cytokine levels, presence of delirium, level of wakefulness during mechanical ventilation or other variables to PTSD outcomes, we may gain insight into causal pathways. Similarly, if medications are hypothesized as 'good' (for example hydrocortisone [9]) or 'bad' (for example benzodiazepines [3]), then ICU investigators can actually test their hypotheses because subjects can be exposed in a randomized fashion to interventions during the stressful interval. Almost no other PTSD field can feasibly do this. At a minimum, critical care studies that are testing interventions that could conceivably alter PTSD outcomes (for example corticosteroids, sedation, and weaning studies) should include some minimal post-ICU PTSD follow-up data to assist stress researchers in developing testable causal models.

Finally, where do we predict that the most fruitful areas of medical PTSD research lie? We predict that they are in the brain [12]. Exciting advances in neuroscience are linking fundamental psychological processes of likely relevance to PTSD such as fear, arousal, extinction, and reward to

anatomical structures such as the amygdala, hippocampus, and prefrontal cortex. On a molecular level, it is plausible that the ICU environment and/or inflammatory stress of critical illness could affect neurotrophins, neurotransmitters, or their receptors, thereby altering memory consolidation and retrieval processes or creating an imbalance between excitatory and inhibitory brain circuits. These changes may be durable and could lead to some of the cardinal symptoms of PTSD. Examining these processes in critically ill patients will require advances in brain imaging or non-invasive measures of brain injury or inflammation embedded in longitudinal studies with high follow-up rates; in our opinion, that is where medical PTSD research needs to go.

### Competing interests

The authors declare that they have no competing interests.

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