

# Morphine May Block PTSD After Serious Injuries

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By **Scott Hensley**

The potent painkiller [morphine](#), one of medicine's oldest drugs, may have a previously unrecognized power to reduce the development of post-traumatic stress disorder in people who've been severely injured.



A Marine walks by an opium poppy in Afghanistan in 2009. (John Moore/Getty Images)

Marines and naval personnel in Iraq who received morphine soon after being hurt badly by roadside bombs, gunshots and other traumas were significantly less likely to be diagnosed later with PTSD than similarly injured soldiers who didn't get the painkiller.

Researchers looked back at medical records of nearly 800 people hurt during a two-year period ending in December 2006. Those with head injuries and some kinds of missing data were excluded. Among the patients who developed PTSD, 61 percent got morphine. Among those who didn't come down with PTSD, 76 percent received morphine.

Why the difference in PTSD? Reducing pain with morphine immediately after injury is "logical conclusion" in explaining the lower rate of PTSD after trauma, the researchers write

The [findings](#) from researchers with the U.S. Navy appear in the current *New England Journal of Medicine*.

In an [accompanying editorial](#), [Dr. Matthew Friedman](#) at the Dept. of Veteran Affairs' National Center for PTSD, writes the findings add to the evidence suggesting that "rapid pain reduction" after a traumatic injury may lower the risk of PTSD.

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## Prevention of Psychiatric Problems among Military Personnel and Their Spouses

Matthew J. Friedman, M.D., Ph.D.

It is always important to capture information generated from clinical databases to advance theory and practice. This is certainly the case with two articles in this issue of the *Journal*. One article addresses the secondary prevention of post-traumatic stress disorder (PTSD) by the administration of morphine during resuscitation and early trauma care in U.S. Navy and Marine Corps personnel injured in combat.<sup>1</sup> The other article describes increased mental health problems among wives of deployed U.S. Army personnel.<sup>2</sup>

The search for a "morning-after pill" after exposure to traumatic stress is obviously of great importance. It would be valuable if it could be established that certain pharmacologic interventions, administered shortly after exposure to traumatic stress, could prevent or reduce the likelihood of the development of PTSD later on. In this issue of the *Journal*, Holbrook and colleagues<sup>1</sup> report that the use of morphine among injured Navy and Marine Corps personnel during early (usually <1 hour) resuscitation and trauma care was significantly and protectively associated with a lower risk of PTSD. This finding adds to a small but growing body of observational and experimental studies that have reported similar results.<sup>3,4</sup> Since physical injury from a traumatic event (especially injury that is associated with severe pain) is a risk factor for the later development of PTSD, such findings suggest a potential for prophylactic use of rapid pain reduction among injured, traumatized persons in both military and civilian acute care settings.

What about persons with minor injuries or no injuries in the aftermath of major trauma who do not need morphine to attenuate physical pain? It is possible that the routine administration of morphine could protect them from subsequent PTSD, but it is unlikely that this could become acceptable in clinical practice. This disorder is understood to develop from Pavlovian fear conditioning in which the adrenergic activation of the amygdala during the traumatic event facilitates encoding of traumatic memories.<sup>5,6</sup> Indeed, microinjections of norepinephrine into the amygdala in rats<sup>7</sup> can enhance fear conditioning, and this response can be blocked by propranolol. Adrenergic activation can also be blocked by morphine operating at mu-opioid receptors located both in the amygdala and the locus ceruleus (which houses most of the brain's adrenergic neurons). Presynaptic inhibitory  $\alpha_2$ -noradrenergic receptors operate synergistically with opiate mu-opioid receptors and also blunt adrenergic activation in both the amygdala and the locus ceruleus.

In short, the thoughtful observations of Holbrook and associates are consistent with current theories about the adrenergic mediation of fear-conditioned traumatic memories. Clearly, the relative contributions of morphine-induced analgesia versus morphine-induced suppression of adrenergic activity must be understood, and the fact that these two mechanisms are not mutually exclusive must be recognized. These results should motivate researchers to redouble efforts to test adrenergic antagonists such as propranolol and clonidine (an  $\alpha_2$ -adrenergic agonist) in the search for a morning-after pill to prevent the later development of PTSD among persons after major trauma.<sup>5,6</sup>

The study by Mansfield and colleagues<sup>2</sup> has a very different focus: the relationship between the deployment of military personnel and the mental health of their wives. Using medical-record data for outpatient care received by more than 250,000 wives of Army personnel (69% of whom had been deployed to Iraq, Afghanistan, or both war zones), Mansfield et al. found that the wives of deployed soldiers, as compared with the spouses of soldiers who were not deployed, had more outpatient visits for depressive disorders, anxiety, sleep disorders, and acute stress reaction and adjustment disorders. Furthermore, deployments of more than 11 months were associated with the use of more mental health services than deployments of 1 to 11 months.

These important findings raise many questions and should serve as an impetus for more fine-grained, hypothesis-driven research. Since the investigators did not have the exact dates of deployment of the soldiers, they could not assess the temporal relationship between deployment and a mental health diagnosis. In other words, was the presence or absence of the soldier more likely to be associated with mental health problems in the wife? If the former, one might consider the literature showing a relationship between spousal distress and marital dissatisfaction associated with deployment.<sup>8,9</sup> PTSD after exposure to combat in male veterans has been associated with distress and the poor psychological well-being of their wives, domestic anger and violence, marital problems due to the numbing and avoidance symptoms of PTSD, a negative effect on parenting, and developmental and behavioral problems among children.<sup>10,11,12</sup> However, if spousal distress was more likely to occur during the deployment itself, one must wonder about the difficulties of being a single parent, constant worry about the safety of the deployed partner, and ongoing behavioral and maturational problems expressed by children dealing with their own concerns about the absent parent.

The answers to other questions should influence policy and clinical practice for the care of spouses and families of military personnel affected by the emotional cycle of deployment. Is it deployment per se, with all the complications of separation and worry about loved ones, that is contributing to more mental health problems? Is the intensity of soldiers' exposure to combat during deployment the critical factor? Is the deleterious effect of deployment on spouses mediated by the presence of PTSD or some other combat-related problem such as physical injury, traumatic brain injury, another psychiatric or substance-use disorder, aggressive or violent behavior, problems expressed by children, other factors, or all of the above? These questions need to be answered. Since social support provides the strongest protection against the development of psychiatric disorders, and since the family is the major source of social support, improvement in the mental health of spouses and children should also pay dividends in improving the mental health of troops throughout the deployment cycle.

The authors of both articles have generated provocative findings from administrative data sets with important implications for preventive strategies. The observations by Holbrook and colleagues on preventing subsequent PTSD by the administration of morphine during resuscitation and early trauma care raise theoretical and practical questions that require rigorous follow-up. Establishing the efficacy of adrenergic antagonists or some other medications as effective prophylaxis against the later development of PTSD would have a considerable effect on emergency medicine for military personnel and civilians. The observations by Mansfield and colleagues on the effect of the deployment of military personnel on the mental health of their wives have public health implications. Besides the obvious importance of developing appropriate programs to fortify wellness and resilience among spouses and children, such

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programs might also be expected to prevent psychiatric morbidity among the troops themselves.

Financial and other [disclosures](#) provided by the author are available with the full text of this article at NEJM.org.

## Source Information

From the National Center for PTSD, Department of Veterans Affairs, VA Medical Center, White River Junction, VT, and the Departments of Psychiatry and Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH.

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