ORIGINAL ARTICLE

# Morphine Use after Combat Injury in Iraq and Post-Traumatic Stress Disorder

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ABSTRACT

**BACKGROUND**

Post-traumatic stress disorder (PTSD) is a common adverse mental health outcome among seriously injured civilians and military personnel who are survivors of trauma. Pharmacotherapy in the aftermath of serious physical injury or exposure to traumatic events may be effective for the secondary prevention of PTSD.

**METHODS**

We identified 696 injured U.S. military personnel without serious traumatic brain injury from the Navy–Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database. Complete data on medications administered were available for all personnel selected. The diagnosis of PTSD was obtained from the Career History Archival Medical and Personnel System and verified in a review of medical records.

**RESULTS**

Among the 696 patients studied, 243 received a diagnosis of PTSD and 453 did not. The use of morphine during early resuscitation and trauma care was significantly associated with a lower risk of PTSD after injury. Among the patients in whom PTSD developed, 61% received morphine; among those in whom PTSD did not develop, 76% received morphine (odds ratio, 0.47; P<0.001). This association remained significant after adjustment for injury severity, age, mechanism of injury, status with respect to amputation, and selected injury-related clinical factors.

**CONCLUSIONS**

Our findings suggest that the use of morphine during trauma care may reduce the risk of subsequent development of PTSD after serious injury.

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Post-traumatic stress disorder (PTSD) is an important and well-documented mental health outcome among seriously injured civilian and military survivors of trauma.[1-10] Increasing recognition of the profound and prolonged detrimental effects on general health status and quality of life when PTSD develops in the aftermath of serious physical injury or exposure to traumatic events has made its prevention a focus of research on trauma-related outcomes.[2-4,11-14] The secondary prevention of PTSD with pharmacotherapy in the aftermath of major trauma is a newly evolving and important area of research.

Current knowledge of the pathogenesis and neurobiology of PTSD provides a strong theoretical basis for the role of pharmacotherapy in the secondary prevention of PTSD after major trauma.[15-17] The primary aim of pharmacotherapy is to decrease or impede memory consolidation and the associated conditioned response to fear after a person goes through a traumatic event.[15,16] This strategy is based on the hypothesis that pharmacotherapeutic agents such as opiates, anxiolytics, and beta-adrenergic antagonists may be effective in preventing the onset of PTSD.[18-23] However, few studies have examined the efficacy of psychotherapeutic medications in the secondary prevention of PTSD that develops in the aftermath of major trauma. Saxe and colleagues reported a protective effect of morphine against the onset of PTSD in children with burn injuries.[24] Studies of other putative psychotherapeutic agents, including benzodiazepines and propranolol, have yielded inconsistent results.[25-28] Little is known about the effect of morphine administration as part of trauma care on the rates of PTSD among seriously injured adults.

The U.S. Navy–Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database (CTR EMED) is a comprehensive prospective clinical database designed to preserve clinical records of casualties incurred in the Iraq military theater both during and outside of battle. We examined the effect of morphine use during early resuscitation and trauma care on the risk of PTSD in injured military personnel, using data from the Navy–Marine Corps CTR EMED.

## METHODS

### STUDY POPULATION

We identified injured military personnel for the study from those who were brought to forward medical treatment facilities (i.e., facilities closest to the point of injury) with injuries incurred during the major combat or support phases of Operation Iraqi Freedom, defined here as the 36-month period from January 2004 through December 2006. Medical treatment facilities located throughout the U.S. Navy–Marine Corps area of responsibility in Iraq provide initial resuscitative treatment for U.S. Army, Navy, and Marine Corps personnel arriving directly from the point of injury, as well as damage-control surgery, additional medical assessment, and stabilization for patients in need of evacuation. During the period from January 2004 through December 2006, these facilities included battalion aid stations (considered level 1 medical treatment facilities), forward resuscitative surgical-system facilities (level 2), and two surgical companies (level 2).

The study was approved by the Naval Health Research Center Institutional Review Board (protocol NHRC.2003.0025) and was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research. The review board waived the requirement for informed consent.

### INJURY-SPECIFIC DATA

Clinical data were obtained from the Navy–Marine Corps CTR EMED.[29] The registry contains information collected from medical encounter forms used at forward medical treatment facilities in Iraq and from clinical records retained at U.S. Army theater hospitals (level 3) and the American hospital (level 4) at Landstuhl Regional Medical Center in Germany. The encounter form, a modified version of the Army Theater Trauma Registry, captures demographic data, time of arrival at the treatment facility, detailed information on the mechanism of injury, and comprehensive treatment data, including medications administered during early resuscitation and trauma care, dosages, route of administration, and interval between arrival at the facility and initiation of treatment. Encounter forms are completed either on paper or electronically by health care providers in the Iraqi theater and are forwarded to the Navy–Marine Corps CTR EMED at the Naval Health Research Center. One purpose of the database is to analyze patterns of combat injury and casualty management from the point of injury through the rehabilitative outcome, with a particular emphasis on the clinical events occurring at or near the point of injury.



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The severity of injuries is assessed by trained clinical staff at the Navy–Marine Corps CTR EMED with the use of the Abbreviated Injury Scale and the Injury Severity Score.[30-32] For the Abbreviated Injury Scale, each injury is assigned to one of six categories based on body location (head, face, chest, abdomen, extremities and pelvis, and skin) and is assessed with respect to clinical severity on a scale of 1 (relatively minor) to 6 (currently untreatable). The Injury Severity Score, which is derived from the scores on the Abbreviated Injury Scale for individual injuries, provides an assessment of overall severity for patients with multiple injuries. The range of scores for the Injury Severity Score is 0 to 75, with 75 indicating the greatest overall severity of injuries.

Of the 790 injured military personnel identified for potential inclusion in the study, we excluded 60 because they had serious traumatic brain injury and 34 because clinical or medication-related data were not complete. The focus of this report is the 696 injured military personnel with complete medication-related data from the Navy–Marine Corps CTR EMED who did not sustain a serious traumatic brain injury. Complete medication-related data were defined as a CTR EMED patient record with medication data coded and entered in the medical record. A serious traumatic brain injury was defined as a head injury with a score of 3 or higher on the Abbreviated Injury Scale and a diagnostic code, based on the *International Classification of Diseases, 9th Revision, Clinical Modification,* of 800.0 to 801.9 (fractures of the vault or base of the skull), 803.0 to 804.9 (fractures at other or unspecified skull sites and multiple fractures of the skull), 850.0 to 854.1 (intracranial injury, including concussion, contusion, laceration, and hemorrhage), or 873.0 to 873.9 (other open wounds of the head).[33] The rationale for the exclusion of patients with serious traumatic brain injury was that the use of morphine in such patients would be both precluded and unwarranted under current Advanced Trauma Life Support protocols. Mild traumatic brain injury (defined as a score of 1 or 2 on the Abbreviated Injury Scale) and the score on the Glasgow Coma Scale on admission to the medical treatment facility were included as covariates in the analysis.

### DATA ON PTSD

We obtained data on diagnoses of PTSD from the Career History Archival Medical and Personnel System[34] and verified them by reviewing medical records documented in the Department of Defense Medical Data Repository. The Career History Archival Medical and Personnel System, which is maintained by the Naval Health Research Center, contains personnel records from the Bureau of Naval Personnel and medical data from the Naval Medical Information Management Center. It includes information on all enlisted members on active duty in the U.S. Armed Forces since 1973. Assessments for PTSD were made from 1 to 24 months after the date of injury and were based on the diagnostic criteria detailed in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).[35] Diagnoses were made by licensed, credentialed providers at both military treatment facilities and private clinics (with government reimbursement), with the use of inpatient and outpatient records. Personnel who were reported to have a diagnosis of PTSD or related symptoms before the designated index injury date were excluded from the analysis.

### STATISTICAL ANALYSIS

Status with respect to a diagnosis of PTSD after injury was the primary outcome variable. The analysis of morphine use during resuscitation according to subsequent PTSD status was made with the use of chi-square analysis, and the association was quantified with the use of the odds ratio.[36] Logistic regression was used to examine the association between the use of morphine during resuscitation and early trauma care, and the later onset of PTSD, with adjustment for injury severity and mechanism of injury, resuscitation, and other clinical factors. A P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

Demographic and clinical characteristics of the 696 injured military personnel included in the study are shown in Table 1. The mean age was nearly identical in the group of 243 patients with PTSD and the group of 453 patients without PTSD. Of the 653 patients for whom data on sex were available, 99% were men. The Injury Severity Score for 90% of injuries was 16 or less; the remaining 10% of injuries, with a score of more than 16, were considered to be serious, and the rates of serious injury were somewhat higher in



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PTSD-negative patients (P<0.05). There were no marked or significant differences between PTSD-positive and PTSD-negative patients for the majority of selected clinical and resuscitation-related variables, including mild traumatic brain injury, score on the Glasgow Coma Scale, intubation, and chemical paralysis with anesthesia. The rate of amputation was higher among PTSD-negative patients (5%) than among PTSD-positive patients (2%), a difference that was small, although significant (P=0.03).

**Table 1. Distribution of Clinical Characteristics in Injured Military Personnel According to PTSD Status.***

| Characteristic | PTSD (N=243) | No PTSD (N=453) |
|---|---|---|
| Age — yr | 24.1±5.9 | 24.3±5.2 |
| Male sex — no./total no. (%) | 199/204 (98) | 445/449 (99) |
| Injury Severity Score — no./total no.(%)† | | |
| <9 | 176/242 (73) | 276/452 (61) |
| 10–16 | 49/242 (20) | 122/452 (27) |
| >16 | 17/242 (7) | 54/452 (12)‡ |
| Amputation — no. (%) | 4 (2) | 24 (5)§ |
| Mild traumatic brain injury — no. (%) | 28 (12) | 41 (9) |
| Glasgow Coma Scale score¶ | 14.6±1.8 | 14.7±1.6 |
| Intubation — no./total no. (%) | 37/204 (18) | 86/449 (19) |
| Chemical paralysis with anesthesia — no./total no. (%) | 33/204 (16) | 74/449 (16) |
| Benzodiazepine use — no. (%) | 28 (12) | 37 (8) |

* Plus–minus values are means ±SD. Data are from the Navy–Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database.[29]
† The Injury Severity Score provides an assessment of overall severity for patients with multiple injuries. The range of scores is 0 to 75, with 75 indicating the greatest overall severity of injuries.
‡ P=0.007.
§ P=0.033.
¶ The Glasgow Coma Scale is an indicator of consciousness ranging from 3 to 15, with 3 signifying deep unconsciousness and 15 normal mental status.

### MECHANISM OF INJURY

The distribution of mechanisms of injury according to PTSD status is shown in Table 2. For all major mechanisms of injury, there were no marked or significant differences according to PTSD status. Major mechanisms of injury for both PTSD-positive and PTSD-negative patients were improvised explosive devices, gunshots, grenades, mortar, and rocket-propelled grenades. Mechanisms of injury and clinical characteristics for all patients included in the analysis did not differ from those in the general patient population represented in the Navy–Marine Corps CTR EMED.[29]

### USE OF MORPHINE AND OTHER PSYCHOTROPIC MEDICATIONS

Morphine use was common in both PTSD-positive and PTSD-negative injured military personnel (in 61% and 76%, respectively). All morphine administration was documented in medical treatment facilities designated as level 1 or level 2, and all morphine was given during resuscitation and trauma care. The transport time from the point of injury to the administration of morphine on arrival at a medical treatment facility was 1 hour or less in 71% of patients. In the study population, doses of morphine (morphine sulfate) were highly standardized, with the modal and median doses equal to 5 mg, and 55% of all morphine doses were between 2 and 5 mg. An additional 33% of doses were between 10 and 20 mg, and doses of more than 20 mg were used infrequently (accounting for only 12% of all doses). The route of administration was intravenous in 98% of patients. The use of other medications with psychotropic effects was uncommon. During resuscitation and trauma care, no patients received serotonin-reuptake inhibitors or beta-blockers. Benzodiazepines were administered to 65 patients (9.3%), however, the use of benzodiazepines was not associated with the onset of PTSD — 12% in PTSD-positive patients and 8% in PTSD-negative patients (P=0.14) (Table 1).

### ASSOCIATION BETWEEN MORPHINE USE AND RISK OF PTSD

Odds ratios and 95% confidence intervals for PTSD according to morphine use are shown in Table 3. The use of morphine directly after injury, during resuscitation and early trauma care, was significantly associated with a reduced risk of PTSD (odds ratio, 0.47; P<0.001). This association remained significant and independent after adjustment for injury severity.

Multivariate-adjusted odds ratios and 95% confidence intervals for the association between morphine use and the risk of PTSD after injury are shown in Table 4, with adjustment for the Injury Severity Score, age, amputation status, mechanism of injury, and presence or absence of mild traumatic brain injury. Morphine use was independently and significantly associated with a reduced risk of PTSD (odds ratio, 0.49; P<0.001). Sex was not a significant factor in the development of PTSD and was excluded from multivariate analysis because of the small number of



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**Table 2. Distribution of Mechanism of Injury among Injured Military Personnel According to PTSD Status.***

| Mechanism of Injury | PTSD (N = 199) | No PTSD (N = 445) |
|---|---|---|
| | *no. (%)* | |
| Improvised explosive device | 82 (41) | 181 (41) |
| Gunshot | 43 (22) | 94 (21) |
| Mortar | 17 (9) | 38 (9) |
| Rocket-propelled grenade | 8 (4) | 36 (8) |
| Other grenade | 12 (6) | 30 (7) |
| Mine | 8 (4) | 16 (4) |
| Fragments from blast — NOS | 4 (2) | 27 (6) |
| Motor vehicle crash | 5 (3) | 7 (2) |
| Fall | 8 (4) | 4 (1) |
| Blunt trauma | 7 (4) | 3 (1) |
| Crush | 0 (0) | 4 (1) |
| Burn | 2 (1) | 2 (0.5) |
| Other | 3 (2) | 3 (1) |

* Totals and percentages vary because of missing or unknown mechanisms of injury in 52 patients (8%). Data are from the Navy–Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database.[29] NOS denotes not otherwise specified.

**Table 3. Unadjusted and Adjusted Odds Ratios for the Association between Morphine Use and the Risk of PTSD.***

| Variable | PTSD (N=243) | No PTSD (N=453) | Unadjusted Odds Ratio (95% CI) | Odds Ratio Adjusted for ISS (95% CI) |
|---|---|---|---|---|
| | *no. (%)* | | | |
| Morphine use | 147 (60) | 346 (76) | 0.47 (0.34–0.66)† | 0.48 (0.34–0.68)† |

* CI denotes confidence interval, and ISS Injury Severity Score.
† P<0.001.

women in the study population. Since the score on the Glasgow Coma Scale is a diagnostic measure of traumatic brain injury, it was incorporated into an alternative multivariate model (model 2), which did not materially alter the findings with respect to the effect of morphine use on the risk of PTSD (odds ratio, 0.66; P<0.05). Since intubation, use of chemical paralysis with anesthesia, and administration of benzodiazepines are closely correlated with one another, we also chose to enter each of these variables separately into multivariate models, controlling for the Injury Severity Score, status with respect to amputation, mechanism of injury, presence or absence of mild traumatic brain injury, and age (model 1). Odds ratios for the association of morphine use with a reduced risk of PTSD were significant and independent in all alternative models. Model 3 included adjustment for intubation (odds ratio, 0.67; P=0.004), model 4 adjustment for chemical paralysis (odds ratio, 0.67; P=0.004), and model 5 adjustment for use of benzodiazepine (odds ratio, 0.50; P=0.002).

There was no indication that the protective effect of morphine use was dependent on the dose. PTSD was subsequently diagnosed in 40% of patients who received low doses of morphine (2 to 9 mg), 40% of those who received moderate doses (10 to 20 mg), and 23% of those who received high doses (>20 mg), with no significant difference in rates according to the dose.

## DISCUSSION

Our study provides suggestive, observationally derived evidence that the use of morphine in trauma care may be protective against the subsequent development of PTSD after serious injury. The use of morphine was associated with a significantly reduced risk of PTSD development in injured military personnel.

Very little is known about the effect of morphine use after serious physical injury on PTSD rates among adults. Our findings are supported by a preliminary study by Saxe and colleagues[24] showing that morphine administration in a small sample of children with burn injuries had a significant protective effect against the development of PTSD symptoms at follow-up 6 months after hospitalization. Bryant and colleagues[37] recently reported that the use of morphine had a significant protective effect against PTSD symptoms in injured adults. The results of the study by Bryant et al. support our findings, although the investigators did not report a significant association between morphine use and a diagnosis of PTSD — the association was only with the severity of symptoms. However, the time frame of PTSD assessment in the study by Bryant et al. was restricted to the first 3 months after injury, and this methodologic limitation may have accounted for the absence of a significant association with the onset of PTSD.

Several reports have suggested that age, sex, and other, injury-related and clinical characteris-



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tics may also play an important role in the development of PTSD after serious injury.[2,7,9,37] In our study, adjustment for age, mechanism of injury, and clinical characteristics such as the Injury Severity Score, amputation status, presence or absence of mild traumatic brain injury, score on the Glasgow Coma Scale, intubation status, and use or nonuse of benzodiazepines did not affect the strength of the protective association between morphine use after injury and the subsequent risk of PTSD. Bryant and colleagues did find that patients with mild traumatic brain injury were at increased risk for the onset of PTSD, but this difference in the results of the two studies may be due to differences in the definitions of mild traumatic brain injury and in the methods used for the assessment of PTSD. More research is needed to determine the potential role of the mechanism of injury, Injury Severity Score, and aspects of resuscitation and clinical treatment in the onset of PTSD after serious injury.

Further evidence that the use of opiates for pain relief as part of trauma care has a protective effect against the subsequent development of PTSD comes from two studies of trauma survivors.[1,38] Norman and colleagues[38] found that self-reported pain levels within 48 hours after serious injury were significantly and strongly associated with the subsequent risk of PTSD, with the risk increased by a factor of 5 at 4 months after injury and by a factor of 7 at 8 months after injury. Similarly, in a study of 2931 seriously injured patients admitted to acute care hospitals in the United States, Zatzick and Galea[1] found that pain after injury was significantly associated with an increased risk of PTSD 1 year after hospitalization. Furthermore, in the recent study by Bryant and colleagues, investigators also found a significant association between the level of self-reported pain and the severity of PTSD symptoms in adults with trauma. The logical conclusion to be made on the basis of these data is that a reduction in perceived pain levels through the use of morphine or other opiates as part of trauma care may lower the rate of PTSD onset after major trauma.

Although much of the research in the field of pharmacotherapy for the secondary prevention of PTSD after trauma is speculative, there is theoretical evidence that early use of anti-anxiety agents can be effective.[1,15-23] Pitman and Delahanty[15] argued that pharmacotherapeutic interventions for the prevention of PTSD will be most effective if medication regimens are implemented after exposure to traumatic events. Morgan and colleagues[39] and other investigators[40] have hypothesized that opiates may interfere with or prevent memory consolidation through a beta-adrenergic mechanism. This theory also lends support to the idea that morphine and other opiates may prove effective in the secondary prevention of PTSD after trauma.

Our study has several limitations that should be taken into account in interpreting the results. First, the study design was observational, and it is therefore not possible to draw causal inferences from the results. Second, data on medication were missing or incomplete for some patients. Consequently, we were unable to include these patients in the present analysis, and it is difficult to speculate on the effect that the absence of some medication data may have had on our results.

A third limitation is that we were unable to thoroughly address the question of a dose–

**Table 4. Adjusted Odds Ratios for the Association of Morphine Use with the Risk of PTSD in Models 1 and 2.***

| Variable | Adjusted Odds Ratio (95% CI) |
|---|---|
| **Model 1** | |
| Morphine use | 0.49 (0.35–0.70)† |
| Injury Severity Score | 1.03 (1.00–1.05)‡ |
| Amputation | 0.40 (0.13–1.22) |
| Rocket-propelled grenade | 0.39 (0.18–0.88)‡ |
| Fragments from blast — NOS | 0.24 (0.08–0.70)§ |
| Mild traumatic brain injury | 1.14 (0.68–1.94) |
| Age | 1.01 (0.98–1.04) |
| **Model 2¶** | |
| Morphine use | 0.66 (0.45–0.97)§ |
| Injury Severity Score | 1.02 (1.00–1.05) |
| Amputation | 0.42 (0.14–1.26) |
| Rocket-propelled grenade | 0.46 (0.21–1.12) |
| Fragments from blast — NOS | 0.30 (0.02–0.88)‡ |
| Glasgow Coma Scale score | 1.03 (0.93–1.14) |
| Age | 1.00 (0.99–1.05) |

* CI denotes confidence interval, and NOS not otherwise specified.
† P=0.02.
‡ P=0.008.
§ P=0.002.
¶ In this model, the Glasgow Coma Scale score was substituted for mild traumatic brain injury.



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response relationship between morphine administration and the risk of PTSD. The morphine doses prescribed for analgesia are highly standardized under current protocols for the treatment of trauma. Although we did not observe any marked or significant trends in the dose–response relationship, it is possible that we were unable to detect such trends because of the small variation in morphine doses.

In conclusion, our findings suggest that the use of morphine after serious injury may be a first-line defense against the development of PTSD. Furthermore, the effect of morphine observed in our study may not be specific to morphine and is likely to be seen with other, related opiates. Our data support the idea that the administration of morphine for optimal control of pain and anxiety after injury may reduce the risk of PTSD.

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