Relationship Between Acute Morphine and the Course of PTSD in Children With Burns

GLENN SAXE, M.D., F.R.C.P.(C.), FREDERICK STODDARD, M.D., DIANE COURTNEY, R.N., KELLY CUNNINGHAM, M.S.W., NEHARIKA CHAWLA, M.A., ROBERT SHERIDAN, M.D., DANIEL KING, PH.D., AND LYNDA KING, PH.D.

ABSTRACT

Objective: To investigate the relationship between the dose of morphine administered during a child's hospitalization for an acute burn and the course of posttraumatic stress disorder (PTSD) symptoms over the 6-month period following discharge from the hospital. **Method:** Twenty-four children admitted to the hospital for an acute burn were assessed twice with the Child PTSD Reaction Index: while in the hospital and 6 months after discharge. The Colored Analogue Pain Scale was also administered during the hospitalization. All patients received morphine while in the hospital. The mean dose of morphine (mg/kg/day) was calculated for each subject through chart review. **Results:** The Pearson product moment correlation revealed a significant association between the dose of morphine received while in the hospital and a 6-month reduction in PTSD symptoms. Children receiving higher doses of morphine had a greater reduction in PTSD symptoms over 6 months. **Conclusions:** This study suggests the possibility that acute treatment with morphine can secondarily prevent PTSD. This result is discussed in terms of the possible effect of morphine on fear conditioning and the consolidation of traumatic memory. *J. Am. Acad. Child Adolesc. Psychiatry*, 2001, 40(8):915–921. **Key Words:** posttraumatic stress disorder, morphine, prevention.

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that represents some of the core features of a child's psychological reactions to such diverse traumatic events as accidents, violent assaults, witnessing violence, natural disasters, medical illnesses, political violence, physical and sexual abuse, and physical injuries such as burns (Famularo et al., 1994; Green et al., 1991; McFarlane, 1987; McLeer et al., 1988; Milgram et al., 1988; Pynoos et al., 1987; Sack et al., 1993; Stoddard et al., 1989). Symptoms of this disorder include intrusive recollections, numbing and avoidance, and hyperarousal (American Psychiatric Association, 1994). PTSD causes tremendous problems for a child's social, educational, and biological development (Cicchetti and Rogosche, 1994; Pynoos, 1993). Evidence indicates that once posttraumatic symptoms become persistent, they can be refractory to treatment (Shalev et al., 1996). Therefore, it is important to identify treatments that may be administered shortly after a traumatic event to prevent the onset of PTSD or inhibit its chronicity. No study has ever identified an effective, secondary preventive treatment for PTSD in children. Given the disabling nature of this disorder and its treatment-refractory nature, it is imperative that treatments that secondarily prevent PTSD be developed. As chronic PTSD may affect the development of the brain (Perry and Pollard, 1998; Pynoos et al., 1997), it is particularly important to prevent PTSD in children.

This study investigates the use of opiate medications as possible preventive agents in children with burn-related PTSD. Children with burns are an ideal population in which to study preventive treatments because (1) they are seen shortly after the traumatic event, (2) they are given numerous medications in the peritraumatic period, and (3) they are at high risk of developing PTSD (Stoddard, 1996; Stoddard et al., 1989). This study assesses the impact, on the course of symptoms, of agents that have great theoretical interest as preventive agents for

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Dr. Saxe is Chairman, Department of Child and Adolescent Psychiatry, Boston Medical Center, Boston University School of Medicine. Dr. Stoddard is Chief of Psychiatry, Shriners Burns Hospital, Boston. Ms. Courtney is with Shriners Burns Hospital, and Ms. Cunningham and Ms. Chawla are with Boston Medical Center, Boston University School of Medicine. Dr. Sheridan is Assistant Chief of Staff, Shriners Burns Hospital, Boston. Dr. Daniel King and Dr. Linda King are research psychologists with the National Center for PTSD, Boston VA Medical Center.

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Reprint requests to Dr. Saxe, Department of Child and Adolescent Psychiatry, Dowling 1 North, One Boston Medical Center Place, Boston, MA 02118.

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PTSD (opiates). Ideally, studies of preventive agents should use randomized and controlled designs. The present study uses a population of children who are already receiving varying doses of these agents. This naturalistic study was conducted in the service of gathering data that may justify a double-blind, controlled study.

Beyond the obvious, pain-reducing qualities of opiates, these medications have direct and potent inhibitory effects on neurological systems known to be important for the development of PTSD. In particular, opiates are known to acutely inhibit the noradrenergic system in areas of the brain hypothesized to be responsible for the consolidation of traumatic memory. Pitman (1989) speculated that the hyperadrenergic state occurring in the wake of a traumatic event is responsible for the overconsolidation of traumatic memory in those who develop PTSD. This overconsolidation of the traumatic memory then becomes manifest in the intrusive memories and reexperiencing of PTSD. The recall of the traumatic event leads to the rerelease of catecholamines and stress hormones that further enhance the traumatic memory. Pitman speculated that this positive feedback loop is responsible for the creation of PTSD and hypothesized that agents that inhibit this hyperadrenergic state may prevent the development of this positive feedback loop.

There is both animal and human research supporting this proposal. Animal research has demonstrated that the adrenergic system enhances memory (Gold and van Buskirk, 1975; Sternberg et al., 1985). It is thought that noradrenergic transmission in the amygdala is critical (Liang et al., 1986). The amygdala is probably the most important structure involved in fear conditioning (Davis, 1990; LeDoux, 1996), which is considered an animal model of traumatic memory and PTSD (Charney et al., 1993; van der Kolk, 1993). Intra-amygdala microinjections of norepinephrine enhance fear conditioning in animals. This fear conditioning is blocked by microinjections of propranolol in the amygdala (Liang et al., 1986). Human studies have demonstrated that adrenergic activity enhances memory for events that involve negative emotions. These studies of college students found that memory for slides accompanied by negatively arousing narratives was enhanced compared with slides accompanied by a neutral narrative. This enhanced memory for negatively arousing narratives was blocked by propranolol (Cahill et al., 1994). These authors reported that enhanced memory for negatively arousing narratives was not present in a subject with bilateral amygdala damage (Cahill et al., 1995). Recent research implicates the adrenergic system in the consolidation of traumatic memory. A study of accident victims in an Israeli emergency room found that heart rate (a marker of adrenergic function) at the time of the trauma predicted PTSD 6 months later (Shalev et al., 1998). In a more recent study of hospitalized survivors of motor vehicle accidents, those who developed PTSD had higher heart rates in the acute posttrauma phase than did those without PTSD (Byrant et al., 2000). Noradrenergic activity has been implicated in individuals with chronic PTSD. Vietnam veterans with PTSD have higher levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of norepinephrine. Agents that stimulate the noradrenergic system, such as yohimbine, cause flashbacks in those with PTSD (Southwick et al., 1993).

There is a great deal of evidence linking morphine, noradrenergic activity, and fear conditioning. Morphine inhibits the locus ceruleus (LC), the main cell bodies responsible for the production of norepinephrine in the brain. There is a high density of μ-opioid receptors on the LC. These receptors are linked to potassium channels with G proteins and have a direct effect on these channels independent of second messengers. Acute administration of morphine leads to a hyperpolarization of the LC through its opening of the potassium channel (Aston-Jones et al., 1993; Christie, 1991; Miyake et al., 1989). Opiate and α_2-adrenoreceptors are also highly co-localized on the amygdala in the rat (Freedman and Aghajanian, 1985). These authors found high co-localization of these receptors in certain parts of the amygdala and, using microionophoresis, found that opiates and α_2-adrenergic agonists similarly inhibited the amygdala. The microinjection of morphine into the amygdala impairs the acquisition of conditioned fear and produces a hypoalgesic response in rats (Good and Westbrook, 1995; Westbrook et al., 1991). Morphine was shown to attenuate the turnover of norepinephrine in stressed rats in two studies (Kohno et al., 1983; Tanaka et al., 1983) but not in a third (Tanaka et al., 1991). It has also been found that morphine depresses the response of the central nucleus of the amygdala to noxious thermal and mechanical stimuli in the rat (Huang et al., 1993).

The literature suggests that morphine blocks the transmission of noxious and fear-enhancing signals at exactly the levels that Pitman (1989) proposed as a potential preventive agent for PTSD. Morphine attenuates noradrenergic activity at the level of the LC and, probably, at the amygdala. It impairs fear conditioning and blocks nox-

ious signals to the amygdala. We thus hypothesize that morphine administered in the wake of a traumatic event will attenuate the consolidation of traumatic memory and prevent the development of PTSD.

Prior to initiating a study in which the morphine dose will be manipulated, we have identified a population of traumatized children who routinely receive morphine during the peritraumatic period. The following study assesses the influence of morphine dose on the development of PTSD symptoms in children with burns over a 6-month period after the burn.

METHOD

Participants

Twenty-four children between the ages of 6 and 16 years with an acute burn were admitted to Shriners Burns Hospital in Boston and were asked to participate in this 6-month follow-up study. All children admitted to the hospital were eligible to participate unless they or their parents did not speak sufficient English to complete the study instruments or they had a medical/surgical condition requiring mechanical ventilation during the hospitalization. The latter exclusion criterion was used because children who are on mechanical ventilators receive much higher doses of opiates, as there is less concern about respiratory compromise in these children. The mean age of the participants was 11.67 years (SD = 3.20); 11 were girls and 13 were boys. The racial makeup of the sample was as follows: 14 of the children were white, 5 were African American, 2 were Asian, 1 was Native American, 1 was Hispanic, and 1 was multiracial. Mean body surface area burned was 11.91% (range = 1%–41%). Ten of the children had surgery for their burn, and the surgery usually involved skin grafting. The average length of stay was 15.60 days (range = 3–48 days).

Procedures

The 24 children who participated were interviewed by one of the investigators as soon as they were medically stable (they did not have delirium, an active infection, etc.). The Child PTSD Reaction Index (CPTSD-RI) (Pynoos and Eth, 1986; Pynoos et al., 1987) and the Colored Analogue Pain Scale (Brigham et al., unpublished, 1996; McGrath and Brigham, 1992) were administered to assess PTSD symptoms and pain, respectively. Children were interviewed an average of 10 days after admission (range = 2–26 days). Upon discharge, arrangements were made for subjects to return to Shriners Burns Hospital for a 6-month follow-up interview in which the CPTSD-RI was again administered. Different investigators conducted the acute and follow-up interviews. The follow-up interviewer was blind to the results of the acute interview.

Measures

Child PTSD Reaction Index. The CPTSD-RI is a 20-item semistructured interview that assesses posttraumatic symptoms in children. Children are asked to rate the frequency of their posttraumatic symptoms on a 5-point Likert scale (0 = never, 4 = most of the time). Interrater reliability is high (Cohen $\kappa = 0.88$). Validity is supported by the finding that children who are known to have PTSD have much higher scores on this instrument. The CPTSD-RI is probably the most widely used measure of posttraumatic symptoms in children. The measure has been used with many groups of traumatized children (Pynoos and Eth, 1986; Pynoos et al., 1987).

Colored Analogue Pain Scale. The Colored Analogue Pain Scale is a pocket-sized visual analogue instrument in which the child slides a marker along a 10-cm line with increasing intensity of red color corresponding to increased intensity of current pain. This instrument has been used with many groups of children who experience pain. Children who are known to have more painful syndromes report higher scores on this instrument than do children with less painful syndromes. Scores on this instrument correlate highly with visual analogue instruments, which are very widely used with populations of children who have pain syndromes. The Colored Analogue Pain Scale has been found to be easier to administer than a visual analogue instruments scale (Brigham et al., unpublished, 1996; McGrath and Brigham, 1992).

Chart Review. During the hospital assessment, information about the child's demographics and hospital treatment was collected from the medical record. Data on surgical procedures, medication administration, and length of hospital stay were collected from hospital records. Mean equivalency doses of morphine and other psychotropic medications, administered in the entire hospital period, were recorded by a research assistant who reviewed the medication administration pages of the hospital record. Entries in the medication administration pages were recorded while the child was in the hospital, by the child's nurse, to document the administration of a medication. The research assistant summed all entries of the dose administered throughout the hospital stay for all opiate and psychoactive medications. These respective sums were divided by the child's weight and the number of days hospitalized for a final mg/kg/day value for each medication administered. As children received opiate medications in various forms (e.g., morphine, meperidine) and through various routes of administration (oral, parenteral), an equivalency dose of oral morphine was calculated by using a protocol from a standard pharmacology textbook (Reisine and Pasternak, 1996).

Data Analyses

The primary independent variable was the equivalency dose of morphine for the child's entire hospital stay (mg/kg/day). The primary dependent variable was the change in CPTSD-RI scores between the in-hospital assessment and the assessment 6 months after discharge. Bivariate correlations were used to determine whether morphine equivalency dose administered while in the hospital was related to the difference in CPTSD-RI scores between the acute and follow-up assessments. This difference can be seen as an index of PTSD recovery. Partial correlations were computed to control for such variables as pain, percentage of body surface area burned, and length of hospital stay.

In addition, to determine whether our main dependent variable, the "change" in CPTSD-RI score, is a robust measure of change, we calculated the reliability of this variable by using the equation proposed by Sharma and Gupta (1986).

RESULTS

The mean CPTSD-RI scores at the acute assessment and at follow-up were 24.80 (SD = 13.90) and 13.10 (SD = 11.02), respectively. Change in PTSD symptoms was determined by the difference between scores at the acute and follow-up assessments for each individual. PTSD symptoms diminished by an average of 13.04 (SD = 14.05)

points over the 6-month period in these 24 children. The reliability of this change score for the 24 subjects was calculated to be 0.78.

Table 1 displays the descriptive information about the burn, morphine dose, change in symptom scores, and demographic information for the 24 children. Specific data with regard to analgesic medications are as follows: All children received opiate medications during their hospitalization. The mean equivalency dose of oral morphine for the 24 children was 0.80 mg/kg/day (range = 0.01–4.50 mg/kg/day; SD = 0.95 mg/kg/day).

The Pearson product moment correlation between hospital morphine dose and change in CPTSD-RI scores was $r = 0.44$, $p < .05$. Thus increased hospital morphine dose was significantly related to a reduction in PTSD symptoms. Figure 1 displays the relationship between the change in CPTSD-RI score between the acute and follow-up assessment and the dose of morphine during hospitalization.

The relationship between morphine dose and change in symptoms was also calculated with control for the variables of body surface area burned, pain, and length of hospital stay. The partial correlation coefficient for the relationship between morphine dose and change in PTSD score, controlling for percentage of body surface area burned, was 0.46 ($p < .05$); the partial correlation coefficient for the relationship between morphine dose and change in PTSD score, controlling for pain, was 0.47 ($p < .05$); the partial correlation coefficient for the relationship between morphine dose and change in PTSD score, controlling for length of hospital stay, was 0.49 ($p < .05$).

We also determined the influence of other psychotropic medications (particularly benzodiazepines) on the change score to assess whether this change is specifically related to morphine. Ten of the 24 children were treated with a benzodiazepine. The various benzodiazepine medications used were translated into equivalency doses of lorazepam. The mean equivalency dose of lorazepam was 0.014 mg/kg/day (range = 0–0.13 mg/kg/day). The correlation between equivalency dose of lorazepam and change in PTSD score was $r = 0.13$, suggesting a very small impact of benzodiazepines on the change in PTSD

TABLE 1
Demographic, Symptom, and Hospital Treatment Variables in 24 Children With Burn Injuries (13 Male and 11 Female)

Subject No.	Age (yr)	Gender	% Body Surface Area	Type of Burn	Acute CPTSD-RI Score	6-Month Change in CPTSD-RI Score	Morphine Dose (mg/kg/day)
1	16	M	14	House fire	6	−2	0.37
2	16	F	15	Car fire	31	−14	1.28
3	15	F	27	Clothes caught fire	28	−19	2.50
4	6	F	41	Hot water spill	36	−4	0.82
5	13	F	27	Grease fire	7	−5	0.32
6	12	M	2	Hot oil spill	33	−4	0.47
7	9	M	20	Explosion	27	−15	0.91
8	10	F	8	Hot water spill	12	0	0.56
9	11	M	20	Playing with matches	10	−2	0.67
10	11	F	4	Hot water spill	16	4	0.27
11	9	F	10	Hot soup spill	21	−3	0.28
12	14	F	2	Grease fire	11	−6	0.38
13	12	M	20	Playing with lighter	36	−6	0.44
14	15	M	5	House fire	16	−7	0.72
15	7	F	8	Hot water spill	15	3	0.22
16	8	M	33	Playing with lighter	50	−30	1.80
17	9	M	5	Hot tea spill	23	−20	0.24
18	16	F	10	Hot water spill	4	1	0.01
19	8	M	4	Scalding	55	−55	0.49
20	7	M	3	Hot coal contact	20	−18	0.65
21	12	F	6	Scalding/steam	40	−29	0.16
22	8	M	27	House fire	43	−38	4.49
23	13	M	2	Explosion	31	−19	0.46
24	13	M	4	Explosion	25	−19	0.42

Note: CPTSD-RI = Child PTSD Reaction Index.

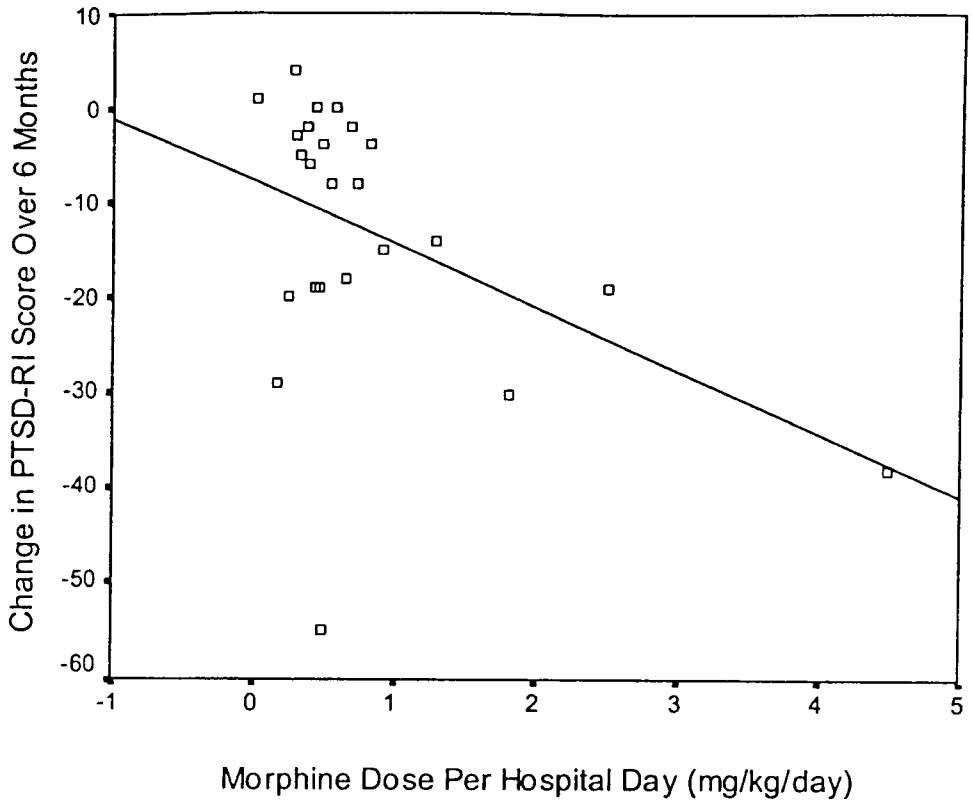

Fig. 1 Relationship between morphine dose during hospitalization and change in posttraumatic stress disorder symptoms over 6 months ($r = 0.44$; $p < .05$). PTSD-RI = Child PTSD Reaction Index.

symptoms over 6 months. The partial correlation of morphine and the change score, controlling for benzodiazepine dose, was 0.42 ($p < .05$).

Frequencies of other psychoactive medications administered to subjects (and their respective doses over the course of hospitalization) are as follows: selective serotonin reuptake inhibitors: sertraline (one child, 0.94 mg/kg/day), paroxetine (one child, 0.35 mg/kg/day); stimulants: methylphenidate (one child, 0.01 mg/kg/day), dextroamphetamine (one child, 0.02 mg/kg/day), pemoline (one child, 1.03 mg/kg/day); anticonvulsants: carbamazepine (two children, 0.63 mg/kg/day and 2.50 mg/kg/day); and α_2-adrenergic agonists: guanfacine (one child, 0.02 mg/kg/day). The infrequency by which these other medications have been prescribed precludes analysis of the correlation between doses and change in symptoms.

DISCUSSION

These results indicate that the dose of morphine administered to this group of 24 children during hospitalization for a burn injury was associated with a significant reduction of PTSD symptoms over a 6-month period. This relationship was maintained after control for such variables as body surface area burned, children's report of pain, and length of hospital stay. Furthermore, doses of benzodiazepines were found to have a very weak relationship to the course of PTSD symptoms, suggesting a specific effect of morphine on this outcome. This later finding of the weak relationship between acute benzodiazepine dose and the course of PTSD symptoms is consistent with data reported by Gelpin and colleagues (1996).

There are a number of possible explanations for these intriguing findings. Morphine treats pain, a psychobiological experience that has been related to PTSD. It is possible that aggressive treatment of pain, indicated by morphine dose, is the mechanism by which PTSD symptoms diminished in this study. Although such an explanation is possible, there is evidence suggesting that it is not the explanation for our findings. Pain during the time of acute assessment was found to be unrelated to the 6-month change in PTSD symptoms. The relationship between morphine dose and change in PTSD symptoms was also present while controlling for the

child's reported level of pain. Although our study design precludes definitive conclusions regarding mechanism, we believe the most likely explanation for the findings involves the effect of morphine on fear conditioning and memory consolidation. As Pitman (1989) has hypothesized, the hyperadrenergic state in the wake of acute trauma leads to enhanced fear conditioning and memory consolidation of the traumatic event. Consistent with this hypothesis, morphine diminishes the hyperadrenergic state by inhibiting the LC and diminishes fear conditioning by attenuating norepinephrine turnover in the amygdala. We believe that this is the most likely explanation for our finding, but it must be tested in larger studies that manipulate the dose of opiates and/or noradrenergic agents such as propranolol or clonidine. Children with burns may be a particularly good population with which to conduct such studies as the hyperadrenergic state is known to occur in these children, by virtue of their physical injury (Wilmore et al., 1974). Future studies of this nature should also specifically examine the relationship between opiate dose, noradrenergic function, and PTSD symptoms.

Our findings may be related to the evolutionary role of opiates. Acutely stressed individuals release endogenous opiates. This stress-induced release of opiates may serve a protective function against PTSD. It is interesting that individuals with PTSD have higher pain thresholds and higher levels of CSF β-endorphin than those without PTSD, suggesting some dysregulation of the opiate system in those with chronic PTSD (Hamner and Hitri, 1992; Pitman, 1989; van der Kolk et al., 1989).

Clinical Implications

Should the relationship between morphine dose and the course of PTSD be replicated, particularly with other samples of acutely traumatized children, these findings may significantly influence clinical practice. As has been mentioned, PTSD tends to be a chronically debilitating disorder in children and adults. The possibility that an agent can prevent the development of PTSD can offer front-line clinicians a powerful tool to diminish psychiatric morbidity in those at high risk. Clinicians who routinely assess acutely traumatized children, such as those who work in emergency rooms, crisis clinics, or in war and disaster zones, may be able to prescribe agents in the peritraumatic period to minimize the risk of PTSD. Although it may not be practical to prescribe morphine in such contexts, morphine shares many qualities with other agents that may be more easily prescribed. As has been mentioned, morphine shares many qualities with α_2-adrenergic agonists. Such agents may prove to be extremely useful for acutely traumatized individuals.

Limitations

The findings presented in this study are intriguing and can potentially have a great impact on clinical practice. This study, however, contains several important limitations. Most important, a relatively small sample size, of a very specific population of children, was assessed. Future studies should assess larger groups of subjects who have experienced a more varied type of traumatic exposure. This study also did not use an experimental design. Doses of morphine were not manipulated, and double-blind controlled designs were not used. The use of experimental designs could more powerfully assess the impact of morphine (or α_2-adrenergic agonists) on the course of PTSD. Future studies should more carefully examine the influence of other variables that may mediate the relationship between morphine dose and course of PTSD. Although we found that morphine dose correlated with the change in PTSD symptoms after controlling for the subject's experience of pain, pain symptoms were assessed on only one occasion. Future studies should assess pain over longer periods of time. In addition, we did not assess the "dose" or quality of psychosocial treatment. It is possible that this factor mediated the relationship between morphine and the course of symptoms. Future studies should measure and control for the possible effect of psychosocial treatment.

Conclusions

The dose of morphine received by children hospitalized for a burn injury was negatively correlated with the course of PTSD symptoms over a period of 6 months. This is the first study to indicate that a psychotropic agent, administered in the peritraumatic period, may prevent PTSD from developing. These conclusions are limited as the sample size was small, an experimental design was not used, and subjects have a particular type of traumatic event (burn injury). Future studies should attempt to replicate these findings by using randomized treatment designs on larger samples of children. Given the difficulties of administering opiates to noninjured children, a possible experimental design might randomly administer morphine as usual and in higher doses to different samples of injured children. Alternatively, as morphine shares

many qualities with α_2-adrenergic agonists on the noradrenergic system, such randomized designs might include agents such as clonidine. It is hoped that this small pilot study will contribute to emerging notions about the possible secondary prevention of PTSD.

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