Conceptually Driven Pharmacologic Approaches to Acute Trauma

By Roger K. Pitman, MD, and Douglas L. Delahanty, PhD

FOCUS POINTS

- There have been few controlled trials of pharmacologic prevention for posttraumatic stress disorder (PTSD).
- One model of the pathogenesis of PTSD implicates stress hormones in the overconsolidation of traumatic memories.
- Propranolol can block the memory-enhancing influence of stress hormones.
- Preliminary studies suggest that a 2–3 week course of propranolol begun in the aftermath of a traumatic event can reduce subsequent PTSD.
- Cortisol can enhance memory consolidation but diminish memory retrieval.
- Preliminary studies suggest that cortisol given to medical-surgical patients during their hospital stays can reduce subsequent PTSD.

ABSTRACT

Secondary prevention of posttraumatic stress disorder (PTSD) entails intervening in the aftermath of a traumatic event to forestall the development of PTSD. There has been little psychopharmacologic research in this area. This is surprising, given that PTSD is the mental disorder with the most clearly identified cause and onset. In a translational model of PTSD's pathogenesis presented herein: A traumatic event (unconditioned stimulus) overstimulates endogenous stress hormones (unconditioned response); these mediate an overconsolidation of the event's memory trace; recall of the event in response to reminders (conditioned stimulus); releases further stress hormones (conditioned response); these cause further overconsolidation; and the overconsolidated memory generates PTSD symptoms. Noradrenergic hyperactivity in the basolateral amygdala is hypothesized to mediate this cycle. Preventing pre-synaptic norepinephrine release with α_2-adrenergic agonists or opioids, or blocking post-synaptic norepinephrine sreceptors with β-adrenergic antagonists such as propranolol, reduces hormonally enhanced memories and fear conditioning. Two controlled studies of trauma victims presenting to emergency rooms suggest that posttrauma propranolol reduces subsequent PTSD, as does one naturalistic clinical study of morphine treatment of burned children. Cortisol both enhances memory consolidation and reduces memory retrieval, leading to mixed predictions. Two controlled studies of intensive care unit patients found that cortisol reduced PTSD. One study did not find benzodiazepines effective in preventing PTSD. Selective serotonin reuptake inhibitors, antiepileptics, and α_2-adrenergic agonists have yet to be tried.

CNS Spectr. *2005;10(2):99-106*

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a serious public health problem. The National Comorbidity Survey[1] estimated the lifetime prevalence of PTSD in the United States at 7.8%. The lifetime prevalence among Vietnam veterans was estimated at 31%.[2] Research has shown that ~69% of non-military respondents reported experiencing a traumatic event in their lifetimes.[3,4] Motor vehicle accidents alone accounted for over 3 million injurious accidents in the US in 1999.[5] Incidence rates of PTSD after motor vehicle accidents range between 19% and 47%.[6,7] Although coming to medical attention less frequently than motor vehicle accidents, interpersonal traumas (rape, assault) often result in even higher rates of PTSD.[3,8]

Little is available in the way of prophylaxis (ie, prevention) for this potentially disabling mental disorder. "Primary prevention" of PTSD involves the prevention of traumatic events. "Secondary prevention" involves intervening in the aftermath of a traumatic event to forestall the development of PTSD. "Tertiary preven-

Dr. Pitman is psychiatrist at Massachusetts General Hospital in Charlestown and the Veterans Administration Medical Center in Manchester, New Hamphire, and professor of psychiatry in the Department of Psychiatry at Harvard Medical School in Boston, Massachusetts. Dr. Delahanty is associate professor in the Department of Psychology at Kent State University in Ohio.

Disclosure: Because there are no drugs with a United States Food and Drug Administration indication for the prevention of posttraumatic stress disorder, all potential clinical applications of currently marketed drugs in the US discussed in this article are "off-label." Dr. Pitman has received grant support from the National Institutes of Health (MH58671 and MH68603). Dr. Delahanty has received grant support from the National Institute of Mental Health (MH062042), and he is on the Ohio Board of Regents. This article was submitted on March 4, 2003, and accepted on November 1, 2004.

Please direct all correspondence to: Roger K. Pitman, MD, Massachusetts General Hospital, Room 2616, Bldg. 149, 13th Street, Charlestown, MA 02129; Tel: 617-726-5333, Fax: 617-726-4078; E-mail: roger_pitman@hms.harvard.edu.

tion" involves interventions designed to reduce symptomatology and disability after PTSD has developed. The current state of PTSD mental hygiene consists largely of tertiary prevention, which is often of limited benefit. Until recently, the most popular secondary preventive intervention for PTSD was psychological debriefing. However, recent reviews[9,10] of controlled studies have failed to confirm its efficacy, and at least one study[11] reported adverse long-term effects. These developments led the United Kingdom Department of Health to go on record that, "Routine debriefing following traumatic events is not recommended."[12]

The collapse of the empirical basis for debriefing underscores the need to find other secondary preventions for PTSD. Treating acute stress disorder with cognitive-behavioral therapy (CBT) has been reported to have preventive value for subsequent PTSD.[13] Secondary pharmacologic prevention of PTSD has received little research attention but is a topic of increasing medical interest.[14] Medical and surgical house officers carry emergency care manuals that include many preventive actions. Examples include prescribing anticoagulants to prevent pulmonary embolism from venous thrombophlebitis and antibiotics to prevent secondary infection in burn victims. In these manuals, it is difficult to find any mention of preventive mental health interventions, including any aimed at acutely traumatized persons.

SIGNIFICANCE FACILITATES REMEMBRANCE

As McGaugh[15] noted, "significance facilitates remembrance." Most everyone is ikely to remember in fair detail where they were and what they were doing on the morning of September 11, 2001. In contrast, few are likely to remember in any detail, if at all, where they were and what they were doing on the morning of September 10, 2001. We are more likely to remember significant life events than trivial ones, and this is surely the result of natural selection. Suppose a hypothetical primitive hominid decided to take a new route to a watering hole, and on her way she encountered a crocodile. Should she fail to remember in the future that a crocodile inhabited that route, she would be more likely to take the same route again and be eliminated from the gene pool.

The Influence of Stress Hormones on Memory Consolidation

Evolution appears to have enabled significance to facilitate remembrance by means of modulatory effects exerted by neurohormones on the consolidation of memory traces, or alternately stated, on the acquisition of conditioned emotional responses. Because emotionally arousing events mobilize neurohormones, facilitation of learning by these hormones amounts to a mechanism whereby the intensity of the unconditioned emotional response to an arousing event regulates the strength of the resultant conditioned response. Evolution favors parsimony; if it can achieve two adaptations through one mechanism, it often will. In the above hypothetical example, the same adrenaline (or epinephrine [EPI]) that enabled the primitive hominid to run away from the crocodile acted in her brain to strengthen her memory of the frightful encounter.

Stress hormones that have been shown to facilitate memory and conditioning in experimental animals include not only EPI, but also corticotropin releasing hormone, adrenocorticotropin (ACTH), arginine vasopressin (AVP), and cortisol.[16,17] Exogenous administration or endogenous activation of these substances shortly following a learning trial leads to the formation of a conditioned response (CR) that is stronger and more resistant to extinction. Their pharmacologic blockade produces the opposite effect. This body of findings[18] represents one of the most exciting discoveries in the history of physiological psychology.

In rats trained in a passive avoidance task, retention is enhanced by systemic post-training injections of EPI.[19] This finding has been replicated in numerous independent experiments. The memory enhancing effect of EPI is counteracted by the pre-training administration of the β-adrenergic receptor blocker propranolol.[20] Post-training administration of systemic propranolol to rats also impairs subsequent memory for a stressful spatial water maze task.[21] Cahill and colleagues[22] found that oral propranolol abolishes the memory-enhancing effect of negative emotional arousal in humans. Although propranolol interferes with sympathetic β-adrenergic transmission both peripherally and centrally, evidence suggests that its central action is responsible for blocking memory enhancement. The β-adrenergic blocker nadolol, which does not cross the blood-brain barrier, does not share this effect of systemic propranolol.[23]

The Role of the Amygdala

The basolateral nucleus of the amygdala (BLA) appears to be the critical brain structure involved in both fear conditioning[24,25] and the memory-enhancing effects of emotional arousal.[26] Post-training intra-BLA microinjections of norepinephrine (NE) enhance conditioning, and this effect is blocked by simultaneous intra-BLA administration of propranolol.[27] β-adrenergic neurotransmission in the BLA is a final common pathway for the influence of most stress hormones on memory, and propranolol acts to block this pathway.[28]

A Translational Model of Posttraumatic Disorder's Pathogenesis

In 1989, Pitman[29] advanced a novel theory of the pathogenesis of PTSD based upon the above animal research into the memory-enhancing effects of stress hormones. Specifically, he postulated that in trauma victims who go on to develop PTSD, the traumatic event (unconditioned stimulus [UCS]) stimulates an excessive release of stress hormones (UCR), which over-consolidate memories of the event (Figure, Loop A), which subsequently manifest themselves in the intrusive recollections and re-experiencing symptoms found in PTSD. Pitman further hypothesized in the same editorial that reminders of the traumatic event (conditioned stimuli [CS]) lead to retrieval of the traumatic memories, with the additional release of stress hormones (CR).[29] These further enhance the strength of the traumatic memory, thereby creating a positive feedback cycle (Figure 1, Loop B). This model regards PTSD as a quantitative overshoot of a normally adaptive mechanism, in which too much significance leads to too much remembrance.

There are several lines of evidence in humans that support the hypothesized pathogenesis of PTSD depicted in Figure, Loop A. The current diagnostic criteria for PTSD require an acute response to the traumatic event of intense fear, helplessness, or horror. Such a response is highly likely to mobilize stress hormones such as EPI. Elevated heart rate in the aftermath of a traumatic event, indicative of a hyperadrenergic state, has been found to predict subsequent PTSD in three[30-32] out of four[33] published studies. The paradoxical finding that quadriplegic injury is less often associated with PTSD than paraplegic injury[34] is potentially explained by the severing of the connection between the brain and the adrenal glands in the former but not in the latter condition. However, challenges to the pathogenic model of PTSD presented here are posed by the viewpoints that PTSD may not be properly regarded as a maladaptive process that occurs immediately following a trauma, but rather as a process involving the lack of resolution of an acute stress reaction; also that PTSD may not involve a normative response to an extreme trauma event, but an rather endocrinologically atypical response.[35]

The hypothetical capacity of conditioned responses to reinforce (rather than extinguish) conditioned responding has been termed "paradoxical enhancement" or "incubation." Eysenck[36] postulated that incubation plays a pathogenic role in human neurosis. Eysenck and Kelley[37] subsequently hypothesized that neurohormones mediate incubation. The notion has recently been reiterated that, "Repeated reactivation and reconsolidation may further strengthen the memory trace and lead to persistence of trauma-related symptoms."[38] Although paradoxical enhancement lacks substantial supporting pre-clinical data, it has a possible neurophysiologic basis in the decreased ratio of inhibitory (medial prefrontal) over excitatory (anterior limbic, amygdala) central nervous functions observed in PTSD.[39] The concept of paradoxical enhancement offers an explanation for the hitherto unexplained, troublesome ability of psychological debriefing in the aftermath of trauma to exacerbate its psychopathological effect.[11]

Implications of the Model for the Prevention of Posttraumatic Disorder

If the model of PTSD's pathogenesis presented herein is applicable, the possibility exists that the disorder can be prevented by pharmacologically intervening in the aftermath of a traumatic event to block potentiation of memory consolidation by stress hormones. Blocking consolidation would be distinct from, but potentially complemented by, preventive cognitive-behavioral therapy, which is likely to act by facilitating extinction. However, the consideration that hormonal influences on memory consolidation are time-dependent processes raises the question as to how soon after the occurrence of a traumatic event a pharmacologic agent would need to be administered to lower the

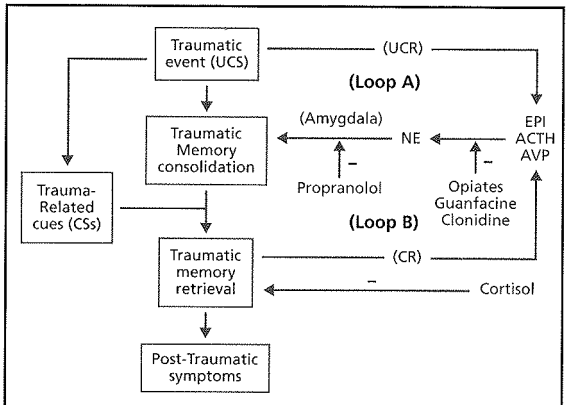

FIGURE. Conceptual Model of the Pathogenesis of Posttraumatic Stress Disorder with Points of Opportunity for Secondary Preventive Psychopharmacologic Agents

UCS=unconditioned stimulus; UCR=unconditioned response; NE=norepinephrine; EPI=epinephrine; ACTH=adrenocorticotropin; AVP=arginine vasopressin CSs=conditioned stimulus, CR=conditioned response.

Pitman RK, Delahanty DL. *CNS Spectr.* Vol 10, No 2. 2005.

risk of PTSD. The finding that injections of EPI administered to rats at intervals of ≥30 minutes following single-trial avoidance training are generally ineffective in strengthening memory[15] would pessimistically suggest that pharmacologic intervention might have to occur sooner after traumatic exposure than would be practical. However, vasopressin given 3-hours post-training has been found to produce a 45% increment in memory performance during subsequent testing.[40] The effect of vasopressin became insignificant after 6 hours, suggesting a wider but still limited window in which pharmacologic agents could be administered. A study that employed positron emission tomography in humans found that it takes 6 hours to permanently store the memory of a newly learned skill in the brain.[41] More recent studies in rats have indicated that there appear to exist several stages of memory consolidation involving different brain regions that may potentially be affected by pharmacologic intervention for a number of days post-training. For example, reversible inactivation of BLA by tetrodotoxin injection 2 days after a single-session acquisition paradigm impairs conditioned freezing responses when measured 48 hours. post-injection. In the case of perirhinal cortex injection, the window of opportunity is a full 8 days.[42]

Importantly, rats are not humans and they do not develop the clinical syndrome of PTSD. One likely crucial difference between a single trial avoidance paradigm in rats and a traumatic event in humans is that humans may replay the traumatic event in their consciousness for variable periods of time after its occurrence.[43] Indeed, this is one of the diagnostic features of acute stress disorder. Re-experiencing may produce sympathetic arousal,[44] and such recurrent arousal may further influence memory consolidation, as suggested in Figure 1, Loop B. Thus, there may be continuing hormonal influences on memory that persist for longer periods (ie, days or weeks) following a traumatic event, which may be amenable to pharmacologic intervention. Ultimately, the question of the window of opportunity for influencing the development of PTSD can only be resolved by clinical trial.

Anti-Adrenergic Agents

Based on the animal research to date, the most promising candidate drug for intervening in the aftermath of a traumatic event to block potentiation of the consolidation of its memory trace by stress hormones is propranolol, which as noted above acts to block post-synaptic β-adrenergic receptors in the BLA. Support for the ability of posttrauma propranolol to attenuate the subsequent development of PTSD comes from two published but preliminary studies.[44,45] Pitman and colleagues[45] recruited 41 patients who presented to a general hospital emergency room (ER) immediately following a traumatic event (mostly motor vehicle accidents). To be eligible, patients had to meet the current diagnostic criteria for PTSD. Patients also had to have a pulse rate ≥80 beats/minute (BPM), presumably indicative of a hyperadrenergic state. The patients were randomized to receive a course of oral propranolol 40 mg or placebo four times daily for 10 days, followed by a 9-day medication taper period. The taper period ended ~12 days prior to the first outcome assessment, so that patients were fully withdrawn from the propranolol at the time of assessment. The first dose of study medication was administered an average of 4 hours after the traumatic event's occurrence. One-month posttrauma, total scores on the Clinician-Administered PTSD Scale showed a trend to be lower in the 11 completers of the course of study medication who had received propranolol, compared with the 20 completers who had not. Based upon their physiological responses during script-driven mental imagery of the traumatic event that had brought them to the ER 3 months earlier, zero of eight propranolol, but eight of 14 placebo, patients were physiologically classified as PTSD (P=.04), which is consistent with a reduced conditioned fear response

In a second, controlled, non-blind, nonrandomized, preliminary study, Vaiva and colleagues[46] recruited 19 patients with HR ≥90 BPM from two ERs in France 2–20 hours following an motor vehicle accidents or physical assault. All were offered propranolol 30 mg TID for 7 days followed by a taper period of 8–12 days. The investigators compared the 11 patients who agreed to take the propranolol with 8 patients who refused propranolol but agreed to participate in the study. The two groups did not differ on demographics, exposure characteristics, physical injury severity, or peritraumatic emotional responses. At 2-months posttrauma, levels of PTSD symptoms were significantly lower in the patients treated with propranolol. Eighty-six percent of the time a patient who took propranolol had a score below that of a patient who did not (P=.04). Both the American and French groups are currently launching randomized clinical trials in larger samples in an attempt to obtain definitive results.

Finally, as described in a single case study,[47] a 44-year-old woman had experienced several prior motor vehicle accidents each followed by months

of PTSD symptoms despite treatment with multiple drugs. Following yet another accident, severe PTSD symptoms again emerged, but these were rapidly and markedly reduced by propranolol started 48 hours after the event.

Another approach to blocking the potentiation of the consolidation of a traumatic memory would be to give pharmacologic agents that act pre-synaptically to reduce NE release. Candidate drugs for this purpose include opioids and the α_2-adrenergic agonists clonidine and guanfacine. Saxe and colleagues[48] performed an observational study of the relationship between the amounts of morphine given to severely burned children and the children's PTSD symptoms. The children who received higher doses of morphine had a greater reduction in PTSD symptoms over a 6-month hospital stay (r=0.44, P<.05). However, an alternate explanation of this finding is that the analgesic properties of morphine reduced the intensity of repeated traumatic CSs such as painful dressing changes. Randomized controlled trials of the ability of opioids to prevent PTSD would appear to be indicated but are likely to be more difficult to implement due to the clinical bar to withholding them when severe pain is involved, and their addictive potential. To date, there have been no reported studies of the use of α_2-adrenergic agonists to prevent PTSD.

This section should not conclude without mentioning γ-aminobutyric acid (GABA) agents, which oppose NE action in the BLA. Some GABAergic drugs have been found to reduce the potentiation of memory by stress hormones.[49] Benzodiazepines, however, are less effective in this regard when administered post- (rather than pre-) training. This limitation may account for the failure to find preventive value for PTSD of clonazepam or alprazolam administered in the acute aftermath of trauma.[50] Nevertheless, given the ready availability of the benzodiazepines, and their current widespread use in psychologically traumatized persons, it would seem that further trials are indicated, either to search for some evidence of their preventive efficacy, or to establish the lack thereof and thereby alter practice patterns. Trials of newer GABAergic agents (eg, gabapentin or tiagabine) that lack some of the undesirable effects of benzodiazepines are also indicated.

Cortisol

At first blush, the model of PTSD's pathogenesis presented herein would suggest that cortisol, which has also been found in animal research to potentiate memory consolidation when given post-training, would be counter-preventive. The situation is complicated, however, by the fact that endogenous hypercortisolemia[51] and exogenous glucocorticoid administration[52] have been found to impair human memory retrieval. Impaired performance in declarative memory tasks has been reported following a dose of hydrocortisone (cortisol) 10 mg.[53]

The ability of cortisol to impair memory retrieval is indicated by an arrow in the bottom right of the Figure. There it will be seen that such an effect has the capability to interrupt positive feedback Loop B. In other words, if PTSD patients' recall of their traumatic events could be reduced by cortisol, the hypothesized re-release of stress hormones that traumatic recall induces, and the resultant paradoxical enhancement of conditioned responding, might be reduced as well.

Cortisol could also work indirectly by containing an overshoot of EPI and other stress hormones. One function of cortisol is to shut down the adrenergic hormones of the "fight or flight" response, preventing their long-term elevation from damaging the body.[54,55] Yehuda and colleagues[56] and Yehuda and colleagues[57] have suggested that during traumatic stress, catecholamine increases are likely to be exaggerated in the presence of a diminished regulatory influence of accompanying cortisol increase. In other words, lower cortisol levels at the time of the trauma may lead to a failure to contain the sympathetic stress response and to consequent prolonged availability of NE in the brain.[58] This may then lead to altered consolidation of memory of the traumatic incident.[59] In animals, low levels of cortisol have been shown to increase the memory-enhancing effects of catecholamines,[60] and high doses of glucocorticoids to decrease these effects.[61]

Two observational studies[62,63] have found that lower posttrauma cortisol levels predict subsequent PTSD. Motor vehicle accident victims who subsequently were diagnosed with PTSD had lower plasma cortisol levels 30 minutes after their accident than victims who subsequently met criteria for major depression.[62] Victims not meeting criteria for either diagnosis had intermediate cortisol levels. Delahanty and colleagues[63] examined the relationship between initial urinary hormone levels and subsequent PTSD symptoms in 99 motor vehicle accident victims. In this study, motor vehicle accident victims were catheterized upon arrival to the trauma unit, and urine was collected for the next 15 hours. Victims who subsequently met acute PTSD diagnostic criteria 1 month after the accident had significantly lower cortisol excretion in the immediate aftermath of the accident than victims who

did not meet diagnostic criteria. In addition, initial cortisol excretion was negatively correlated with subsequent symptoms of PTSD (r=–.46, P<.01).

Schelling and colleagues[64] have found that exogenously administered stress doses of cortisol reduce the development of subsequent PTSD in medical-surgical patients. An initial retrospective case-control analysis revealed that septic shock patients who received hydrocortisone 100 mg bolus during the sepsis episode followed by 0.18 mg/kg/hour until shock reversal had a significantly lower subsequent incidence of PTSD than patients who received standard treatment for their septic shock. These findings were replicated in a randomized, double-blind study.[65] During a sepsis episode, 11 patients were randomly assigned to receive placebo, and nine were assigned the abovementioned dose of hydrocortisone for 6 days. Results revealed that only 1 of 9 from the hydrocortisone group but 7 of 11 from the placebo group (P=.02) met PTSD criteria assessed 31 months after discharge from the intensive care unit. However, interpretation of this finding is confounded by the observation that the placebo patients required higher amounts of NE for blood pressure support. Thus, the exogenous cortisol could have acted indirectly to prevent PTSD by reducing total exogenous NE requirement.

More recently, Schelling and colleagues[66] examined the efficacy of peri-and post-operative exogenous hydrocortisone in preventing PTSD symptoms in patients following cardiac surgery. Twenty-six patients received a loading dose of hydrocortisone 100 mg followed by a continuous infusion of 10 mg/hour during post-operative day (POD) 1. Patients received 5 mg/hour on POD 2, and dosing was tapered to 20 mg TID on POD 3 and 10 mg TID on POD 4. Twenty-two comparison patients received standard treatment. Results revealed that the patients who received the hydrocortisone regimen reported significantly fewer PTSD symptoms than comparison patients (P<.05).

Other Candidate Agents for the Prevention of Posttraumatic Stress Disorder

In this review, emphasis has been given to possible preventive agents suggested by one translational model of PTSD's pathogenesis highlighted here. However, at least two other models[67-69] suggest other potential agents, although these will only be briefly mentioned. The neurophysiological kindling model of PTSD suggests that anti-kindling agents (ie, antiepileptics) in addition to having some therapeutic value,[67] may also have preventive value. The stress- and cortisol-induced neurotoxicity model of PTSD[68,69] suggests that drugs that have been found to block stress-induced hippocampal damage, including antiepileptics (eg, phenytoin[70]) and selective serotonin reuptake inhibitors (eg, tianeptine[71]) and possibly even anti-cortisol drugs (eg, mifepristone) may also be useful in preventing PTSD.

EFFICACY VERSUS EFFECTIVENESS

This article has discussed several promising secondary preventive pharmacologic interventions for PTSD, although their efficacy needs to be further tested in larger, randomized controlled trials. Even if the efficacy of one or more of these interventions becomes established through further research, this will not equate with effectiveness, which involves the application of the intervention in usual clinical settings. Obstacles to effectiveness include patients' psychological reluctance to accept acute posttraumatic psychiatric interventions, and their proneness to drop out before treatment is completed.[72] However, this may be less problematic in clinical than in research settings. In research settings involving placebo-controlled trials, the investigator can only offer the patient the possibility of receiving a drug that may be efficacious. Once a drug has proven efficacious in clinical trials, however, the clinician can confidently offer a drug that is likely to be helpful. Another obstacle is posed by medical contraindications to the administration even of an efficacious drug. Propranolol, for example, may not be able to be safely administered to patients with asthma or heart block, or in situations in which it is clinically necessary to rely upon the sign of tachycardia to disclose the development of a medical complication such as hypovolemia or hypoglycemia. Cortisol may not be able to be given to patients with penetrating wounds that pose a risk of infection. It may turn out, however, that demonstration of the efficacy of one of these, or other, agents would spur the development of new drugs that retain efficacy with fewer contraindications. An example might be a β-blocker with the high capacity to cross the blood-brain barrier of propranolol but lacking in the latter's asthmagenic effect.

CONCLUSION

This review has highlighted a number of possible pharmacologic interventions that could be implemented in the aftermath of traumatic events to prevent or reduce their potentially psychiatric consequences. A recent MEDLINE search on PTSD yielded 7,500 articles, only five[45,46,50,65,66] involved a prospective, controlled, preventive, pharmacotherapeutic clinical trial. Moreover, these studies are

properly regarded as preliminary. A recent review noted, "To date there is almost no empirical data on effective pharmacologic interventions in the immediate aftermath of extreme psychological trauma.... Controlled trials are essential given the limited information in this field."[73] CNS

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