Can Posttraumatic Stress Disorder be Prevented?

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ABSTRACT

After trauma, it is often possible to prevent, or at least reduce the effect of, certain medical sequelae if intervention occurs within a particular time period: "the golden hour(s)". The possibility of a similar window of opportunity in posttraumatic stress disorder (PTSD) is discussed here. The essence of acute distress management should be to help contain and attenuate emotional reaction, and to encourage a return to full function and activity. Early intervention at this point could prevent the subsequent development of PTSD. Preclinical and clinical data suggest that amnesia of the traumatic event is associated with a decreased prevalence of PTSD, and that debriefing is not necessarily beneficial. Randomized, placebo-controlled studies are needed in order to examine what psychological and/or pharmacological interventions should or should not be made during the "golden hours" following trauma.

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Needs Assessment

As posttraumatic stress disorder (PTSD) is triggered by an identifiable event, the opportunity presents for interventions in the aftermath of trauma with the aim of preventing the development of PTSD. It is also important that patients are made aware that most cases of acute stress reaction improve without intervention. Clinicians should be aware of what is and is not recommended in the hours following trauma exposure, and should understand the directions of research exploring possible preventions for PTSD.

Learning Objectives

At the end of this activity, the participant should be able to:

- Describe the typical recommended treatment of a patient presenting after trauma
- Differentiate between symptomatic and preventive interventions in the acute stress reaction phase
- Discuss possible methods for preventing PTSD, such as disrupting memory consolidation or early use of selective serotonin reuptake inhibitors

Target Audience: Psychiatrists

INTRODUCTION

After a trauma, certain medical sequelae can be ameliorated or even prevented if intervention occurs within a particular window of opportunity. This window of time has been given the euphemism "the golden hour(s)," as intervention in that time is particularly effective. Several examples of this are well established. For example, in thrombotic cerebular vascular accident, there is a 3-hour window from the onset in which clot-busting drugs can be administered to relieve the thrombosis. In heart attack, reperfusion of the infarct-related artery in the first hour significantly reduces mortality rates. The principle is that immediate intervention is given in order to prevent/decrease the impending (usually devastating) sequelae of those events, which often trigger a chain of pathological processes. If the right intervention is given during the window of opportunity, it might dramatically improve outcome.

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Is there a golden hour in psychiatry? Can intervention right after exposure to traumatic events attenuate the pathological response that we refer to as posttraumatic stress disorder (PTSD)? Along these lines, this paper examines whether or not usual emergency room practice actually prevents or reduces the risk of developing PTSD later on.

RISK FACTORS FOR PTSD

Although PTSD is clearly precipitated by trauma exposure, differences in exposure do not fully determine either the development of or recovery from PTSD. In recent years, there has been a growing interest in identifying biological and clinical risk factors that increase the likelihood that PTSD will develop following trauma exposure. These have ranged from genetic to environmental factors, and have included both pre-existing traits, characteristics of the traumatic event, and aspects of the victim's peri- and post-traumatic response. Correspondingly, factors with the potential to reduce the risk have been identified and the concept of "resilience factors" has been proposed.[1,2]

Although little is known about predictive factors of PTSD and the immediate response to the trauma, the symptoms that were found to be associated with higher frequency of PTSD include, among others, a significant panic-like response, pronounced distress, dissociative response, and past history of anxiety or depression. Those symptoms may reflect the intensity or severity of the current experience, a pre-existing individual trait, or sensitization from prior trauma exposure.

The risk factors named above could certainly reflect expressions of either genetic diatheses or early life experiences. For example, early abuse might lead to changes in personality and cognitive abilities, but may also be a consequence of these factors. Similarly, factors associated with heritable parental characteristics (eg, psychopathology) may increase risk for PTSD by increasing exposure to neglect or abuse.

TABLE 1.
Goals of Acute Stress Management: Ra, Rb, Rc

1. **R**eturn to full **a**ctivity/functioning
2. **R**egain **b**ehavioral/emotional control
3. **R**estore interpersonal **c**ommunication

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ACUTE DISTRESS MANAGEMENT

The essence of acute distress management should be to help contain and attenuate emotional reaction. The goal is to help the traumatized person regain emotional control, restore interpersonal communications, and encourage the return to full function and activity. The goals of acute stress management are summarized in Table 1.

In order to achieve these goals, it is necessary to address basic needs, such as reducing the exposure to the stress (eg, finding a secure place), reducing pain, taking care of physiological needs (eg, food, drink, hygiene), providing information/orientation, recruiting resources such as friends or family members to provide support, and emphasizing the expectation of returning to normal (eg, assuring, "This is a normal response to an abnormal situation, and you will do fine") (Table 2).

At this stage it would be important not to pathologize (eg, talk about "fright" instead of "panic"), and to emphasize the importance of returning to normal routine. The focus is on information, orientation, and expectation of returning to normal, and not on the emotional component. Along those lines, group therapy, which might lead to emotional reaction, should be used with great caution, if at all.[3,4] It is also recommended, at this point, not to give pharmacological intervention to reduce the acute stress symptoms (eg, benzodiazepines [BNZ] to reduce acute anxiety), except in very extreme stress reaction.[5-8]

It might be advisable to not routinely initiate professional contact, in order to not pathologize the response and to encourage, rather than interfere with, the normal spontaneous recovery process. Only in severe cases (eg, prolonged dissociative state, prolonged panic-like response) might it be recommended to continue the treatment (Table 3).

CAN PTSD BE PREVENTED?

It is feasible that intervention (psychological or pharmacological) in the immediate aftermath

TABLE 2.
Addressing Basic Needs via ERASE

Reduce **E**xposure to stress (eg, finding secure place)
Restore physiological needs (food, drink, hygiene)
Provide **A**ccess to Information/orientation
Locate source of **S**upport. (eg, family, friends)
Emphase the **E**xpectation of returning back to normal

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of exposure to trauma might play a determining role in the evolution of the response, increasing or decreasing the risk of PTSD.

Preclinical and clinical data suggest that amnesia of the traumatic event is associated with a decreased prevalence of PTSD. Clinical data include following up on traumatic brain injury and examining the frequency of PTSD in individuals with amnesia as compared to non-amnestic patients. Klein and colleagues[9] examined 120 patients with mild traumatic brain injury. Patients' memory of the traumatic event was recorded (24-hours post trauma), and they were assessed for PTSD symptoms 1 week, 3 months, and 6 months later. Rates of PTSD 6 months after the traumatic event were found to be significantly lower in patients with no memory of the traumatic event (6% PTSD) than in patients with memory of the event (23% PTSD).

AN INNOVATIVE ANIMAL MODEL OF PTSD

Animal models of psychiatric disorders have been useful in elucidating associations between behavioral symptoms and biological abnormalities and in suggesting possible treatment strategies for psychiatric disease.[10] The rationale behind careful and approved use of animal models for human conditions is to enable experimentation in ways and with sample sizes that are impossible in humans for ethical/moral or practical/technical reasons. For the animal model to be useful, it must be as valid an approximation of the human disorder it is modeling as possible, while always keeping in mind the risks inherent in "overhumanizing" animal behaviors.

Animal models have been developed in which intense stressful experiences, aversive challenges, and situational reminders of a traumatic stress have been shown to result in long-term effects.[11-23] Psychological and physiological functioning, as reflected in biobehavioral tests that mimic many of the changes seen in PTSD in human subjects, have been reported. These models include inescapable electric (foot) shock,[11,12] social confrontations,[13] underwater trauma,[14] and exposure of a rodent to a predator.[15,16,18-23] Most models have dealt with single exposure, but a minority also used stress-restress paradigms or time-dependent sensitization.[24]

Irrespective of the study design/model or the stress paradigm, the exposed animals displayed a diverse range of responses, and yet the results were presented, discussed, and conceptualized as involving the entire exposed population versus controls (ie, not exposed). The clinical syndrome, however, clearly affects only a proportion of the exposed[25] and therefore reflects the fact that different subjects respond differently. The consequences of exposure to extreme events range from normal adaptive responses, which take some time to resolve, to unremitting (maladaptive) extreme psychophysiological stress dysregulation, ie, PTSD. The syndrome of PTSD thus revolves around differential degrees of responses, which probably reflect differential vulnerability or resilience. Because animals display a range of responses after exposure to trauma, it is clear that some animals appear to be more vulnerable than others to biobehavioral responses to stress, and it is therefore justifiable to focus on the differential response, ie, setting apart the markedly affected from the slightly affected and studying only the "obviously" or "markedly" affected.

In this model, rats were exposed to a predator scent (urine) for 10 minutes, as previously described.[15,16,19-23] Seven days after a single 10-minute exposure to the predator scent, exposed rats showed significantly increased levels of avoidance and anxiety-like behavior in the plus-maze paradigm, as previously found by Adamec and colleagues[15-17,19] and Cohen and colleagues.[20-23] The exposed animals also exhibited higher mean startle responses than did the control rats. However, the animals' behavior was not uniformly disturbed but rather demonstrated a broad range of variation in severity of anxiety-like behaviors. Variations emerged in the behavioral response after exposure to trauma: some rats were minimally affected and others were highly affected. The variation in behavioral response among a genetically uniform group of rats suggests early individualized environmental factors are relevant in this disorder. With the assumption that not all animals in a given population exposed to a trigger in a stress paradigm will respond to an identical degree (like humans exposed to traumatic events), the variance in behavioral expression was made the focus of the study.

TABLE 3.
What Not to Do: *The 4Ps*

Do not **P**athologize
Do not **P**sychologize (ie, do not facilitate emotional reaction via group therapy, debriefing, etc.)
Do not **P**harmacologize
Do not push for **P**rofessional contact

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This is because the focus of PTSD research is not on all the individuals exposed, but only on those who have a pathological response.

CUT-OFF BEHAVIORAL CRITERIA

Based on the fact that the group is not homogeneous, but tends towards a bimodal rather than a normal distribution, the animals were classified according to the extent of behavioral change. One possibility is to design and apply something akin to the diagnostic inclusion and exclusion criteria used in clinical studies. The idea is to construct a set of criteria in animal studies of stress to set apart the affected, or maladapted, animals from their well adapted counterparts. In this model two consecutive behavioral criteria were used, each representing a diagnostic cluster (as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition): fearful behavior on the elevated plus maze (as a behavior representing avoidance) and startle reaction (as a symptom of hyperarousal and nonhabituation response to acoustic stimulus) in the acoustic startle response paradigm. The plus maze and acoustic startle response paradigms were selected to constitute the basis for the cut-off behavioral criteria (CBC) for a number of reasons: First, each has been shown to be a valid measure of stress responses in numerous studies; second, they are each well defined and straightforward to score.

Maladaptive responses to both of these serial CBCs were required for "inclusion" in the study group. By employing those two serial behavioral tests to define the maladaptive animals, the degree of individual differences between animals in the study population was reduced. It is suggested that this approach might reflect a more valid population of affected animals and therefore might parallel patients who fulfill criteria for PTSD in human studies more closely.

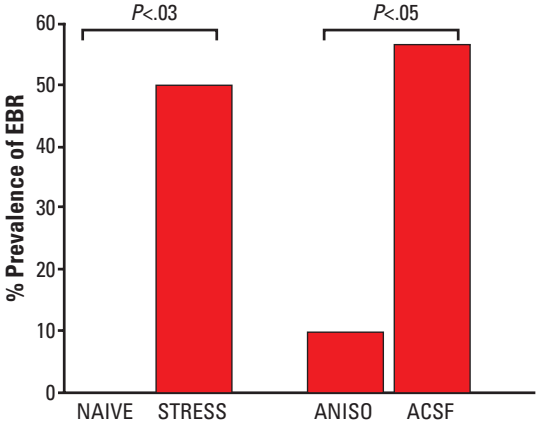
To define the affected population, the following CBCs were determined for maladapted animals: (1) 5 minutes spent in the closed arms of the elevated plus maze and 0 open-arms entries (without a decrease in total exploration activity); and (2) mean amplitude of the startle response (110 Db) >800 and nonhabituation of the acoustic startle response. The following CBCs were determined for well adapted animals: (1) 0–1 minutes spent in the closed arms of elevated plus maze and ≥8 open-arms entries; and (2) mean amplitude of the startle response (110 Db) <700 and normal habituation of the acoustic startle response.

When behavioral data for the entire exposed population were examined by this means, based on the segregation of animals according to the CBCs, only ~22% demonstrated significant behavioral disruptions as the result of exposure to the stressor compared to 1.3% of the controls. Based on this framework, a variety of intervention trials are possible. Just as exposed rats can be compared behaviorally to non-exposed rats, treated rats can be compared to non-treated, different doses can be compared, and early intervention with a given compound can be compared to no intervention.

INDUCTION OF AMNESIA AND PTSD

To examine the effect of memory on PTSD, a study of anisomycin (a protein synthesis inhibitor that blocks memory consolidation) was carried out in this animal model.[26] In this study, the protein synthesis inhibitor anisomycin was effective when administered within 1 hour after exposure (Figure 1), but not when administered later on (after reactivation of the trauma by a trauma cue). Not only does this study support the association between memory and PTSD, but the effect of the timing of the dose suggests that the intervention needs to be swiftly administered in order to prevent consolidation of the memories.

FIGURE 1.
Prevalence of Extreme Behavioral Response After Trauma in Rats Compared to Non-exposed Rats (Left) and a Comparison of Early Anisimycin Treatment to Placebo Treatment in Those Exposed (Right)[26]



EBR=extreme behavioral response; ANISO=anisomycin; ACSF=artificial cerebrospinal fluid.

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AMNESIA, REPRESSION, AND PTSD

Along these lines, psychological defense mechanisms which mimic amnesia (like repression) would be predicted to be useful. Indeed, a study of repressive coping styles after myocardial infarction showed this to be the case.[3] In this study, 116 myocardial infarction patients were assessed for repressive coping style within a week of their myocardial infarction, and based on this they were divided into four groups: high anxious, low anxious, defensive, and repressors. Patients were also assessed at this point for symptoms of acute stress disorder (ASD), and after 7 months for symptoms of PTSD. The repressors group displayed fewer symptoms of both ASD and PTSD, implying that repression is indeed useful in buffering against the potential consequences of trauma.

DEBRIEFING, AMNESIA, AND PTSD

Psychological intervention that enhances the traumatic memory is predicted to be associated with less favorable outcome. Indeed, a single-session debriefing—a session that often leads to reconstruction of the trauma—as found to be associated with a less positive outcome as compared to non-intervention, or is at the least ineffective. A randomized controlled trial in which some traffic accident victims were given a single one-hour debriefing intervention, and others had no intervention was followed up after 4 months and again after 3 years. At 4 months, the intervention group was found to have marginally (though mostly non-significantly) poorer outcome,[27] while after 3 years, measures of psychiatric symptoms, travel anxiety, and level of functioning were all significantly worse for patients in the intervention group.[28] The findings led the authors to conclude that psychological debriefing is not beneficial and may in fact be detrimental.

In a recent laboratory trial, participants were shown a video of paramedics at the scene of a car accident, including the disfigured face of a victim (high stress, n=58) or a similar video that also included a close-up shot of a disfigured face (low stress, n=61).[29] Half of each group was then debriefed, the other half not. This study found that subjects in the high-stress group reported more distress, avoidance, and intrusions at a 4-week follow-up than did subjects in the low-stress group. More importantly, debriefing was found to have a detrimental effect on the high-stress group, who reported significantly more distress than the non-debriefed members of this group. Although this study does not involve life-threatening trauma, nor does it diagnose PTSD, the results imply that debriefing may serve to exacerbate distress following a traumatic experience.

Sijbrandij and colleagues[4] carried out a further study on debriefing in which trauma survivors were given emotional debriefing (n=73), educational debriefing (n=70), or no intervention (n=81), 2 weeks after the traumatic event. Follow-up was carried out at 2 weeks, 6 weeks, and 6 months following the intervention. This study showed that although scores on PTSD, anxiety, and depression measures decreased over time, there was no significant difference between the groups on any of the measures. Although debriefing was not found to be effective in any of the studies described here or in a meta-analysis carried out on other debriefing studies,[30] this study implies that it is in the immediate aftermath of the trauma that debriefing is potentially detrimental, as no effect was found for debriefing 2 weeks following the event.[4] It seems as that, in line with the "amnestic hypothesis," psychological interventions that interfere with the amnesia/repression process should not be used routinely, as they might impede the powerful spontaneous recovery process.

MEMORY CONSOLIDATION AND PHARMACOLOGICAL INTERVENTION

This line of reasoning suggests that pharmacological intervention that is associated with a decrease in consolidation of the traumatic memory might be beneficial and vice versa—interventions that are associated with an enriching of the traumatic memory are hypothesized to be associated with a worse outcome.

Early administration of BNZ was found to be associated with a less favorable outcome in two small studies.[5,6] In the first, 13 trauma survivors treated with BNZ for 1–6 months had significantly more PTSD at a 6-month follow-up than 13 untreated matched control patients.[5] The second study reported 55% PTSD in patients treated with BNZ for 6 weeks, as compared to 27% in a control group.[6] Data supporting this trend was also found in the animal model of PTSD described above. In this study,[31] although both early and late administrations of BNZ (alprazolam) were associated with decreased anxiety in the short-term, their long-term behavioral response was different. Only the early-BNZ group displayed an increase in PTSD-like behavior (as expressed by the anxiety scale) when the rats were exposed a month later to the traumatic cue.

One possible explanation for these sequelae of early BNZ administration might be related to its

effect on the hypothalamic-pituitary-adrenal (HPA) axis; BNZ abolishes the cortisol response (which is usually associated with trauma exposure) and therefore might attenuate the natural response—increased cortisol levels, an increase associated with a decrease in the fear index.[32]

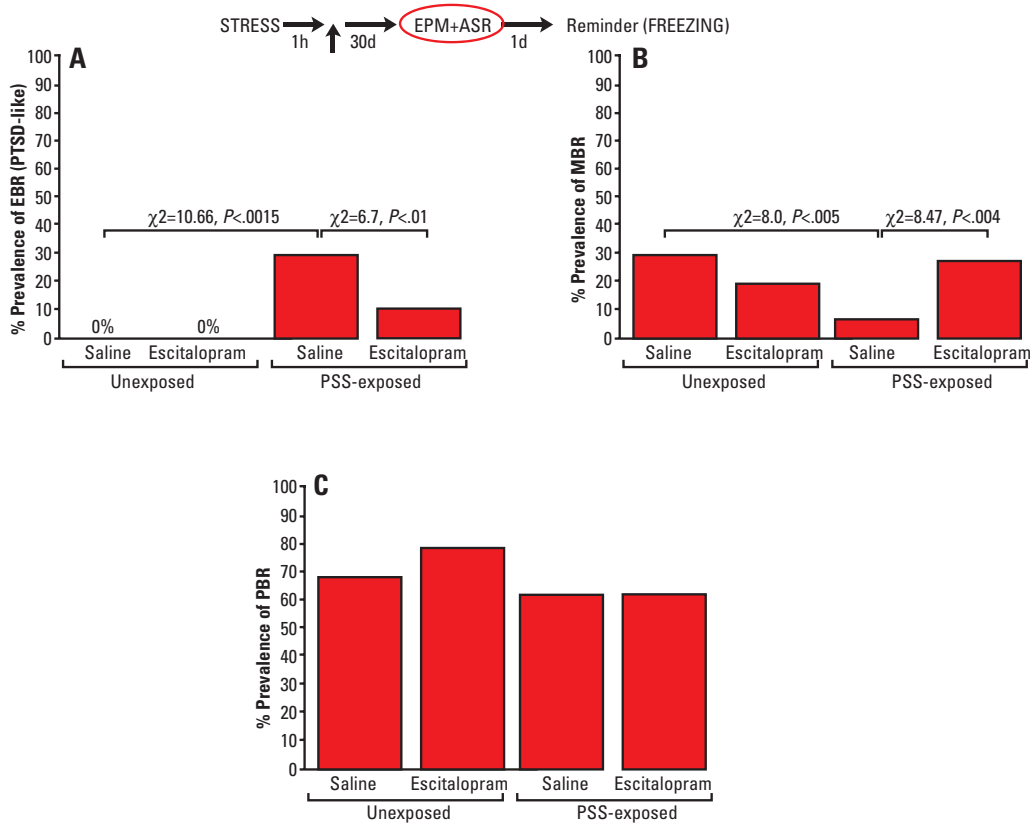
Indeed, the HPA axis is the major constituent of the neuroendocrine response to stress. Some clinical studies[33,34] have suggested that cortisol administration might be associated with a reduced risk of developing PTSD. However, this hypothesis has not yet been studied properly in PTSD. A study that looked at early administration of different doses of cortisol in the abovementioned animal model of PTSD demonstrated a U-shaped dose effect of post-stressor administration of corticosterone in Sprague-Dawley rats on changes in behaviour. In this study[35] 0, 1, 3 and 5 mg/kg cortisol led to more animals with PTSD-like behaviour, while cortisol 25 mg/kg led to significantly less PTSD-like behavior as measured 1 month later when a cue reminder was administered.

Other possible interventions that might be considered for PTSD prophylaxis are the use of medications that act to suppress catecholamine activity of sympathetic arousal, such as proponalol and guanfacine. However, neither has been shown to prevent PTSD.[36,37] In one randomized trial, propranolol reduced the incidence of the development of PTSD-related psychophysiological alterations.[38]

EARLY ADMINISTRATION OF SSRI AND PTSD PREVENTION

The only medications with a specific indication for PTSD are selective serotonin reuptake inhibitors (SSRIs)—namely, sertraline and paroxetine. However, these were only tested several months

FIGURE 2.
Prevalence of Extreme Behavioral Response (A), Minimal Behavioral Response (B), and Partial Behavioral Response (C) to Stressor in Exposed and Unexposed Rats Treated with Escitalopram or Placebo 1 Hour after Exposure[39]



EBR=extreme behavioral response; ASR=acute stress reaction; PSS=predator scent stressor; MBR=minimal behavioral response; PBR=partial behavioral response.

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(and in many cases years) after the exposure. Would an early administration of SSRIs immediately after the exposure have a preventive effect? The potential role of SSRIs in hippocampal neurogenesis[39] along with open naturalistic clinical observations paved the way to examining this question in an animal model of PTSD.[40] The results were quite promising, and suggested that early administration of SSRI (sertraline, in this case) was associated with a significant decrease in PTSD-like behavior (Figure 2).

Currently, this is being studied in a double-blind, random-assignment study with the aim of including 100 patients in each arm. This study provides an example of a study design formulated to test potential early interventions in PTSD (Figure 3).

Although this study involves early pharmacological intervention, it should be noted that the intervention given is not for the treatment of acute stress symptomatology, but rather is an attempt to prevent later development of PTSD. Along the same lines, the professional contact required for the follow-up of this study is merely for the assessment of symptoms as they stand, and not for their specific treatment. In fact, if preventive treatments are found, it would still be important to emphasize to patients that the administration of the preventive medication and the necessary professional monitoring do not mean to pathologize the patient's current state, and the expectation is still a return to full function.

CONCLUSION

The results of studies such as early cortisol administration, early SSRI administration, and others might shed some light on the intriguing question, "Can PTSD be prevented?" These kinds of studies—randomized, placebo-controlled studies that are powered to answer this question—are needed to examine what psychological and/or pharmacological interventions should or should not be made during the "golden hours."

Ultimately, PTSD prevention, via either pharmacological or psychological mechanisms or a combination of both, may require the identification of a broader range of factors, including genetic or epigenetic modifications that underlie failure of reinstatement of physiological homeostasis. Potential targets for future intervention may be neurogenesis, HPA axis, and other factors that enhance resilience, whether through decreasing the impact of the traumatic memory or via other, yet to be explored, mechanisms. In any event, it seems that the type of intervention in the "golden hours" in PTSD might be a key element in the odyssey to find out how PTSD can be prevented. ***CNS***

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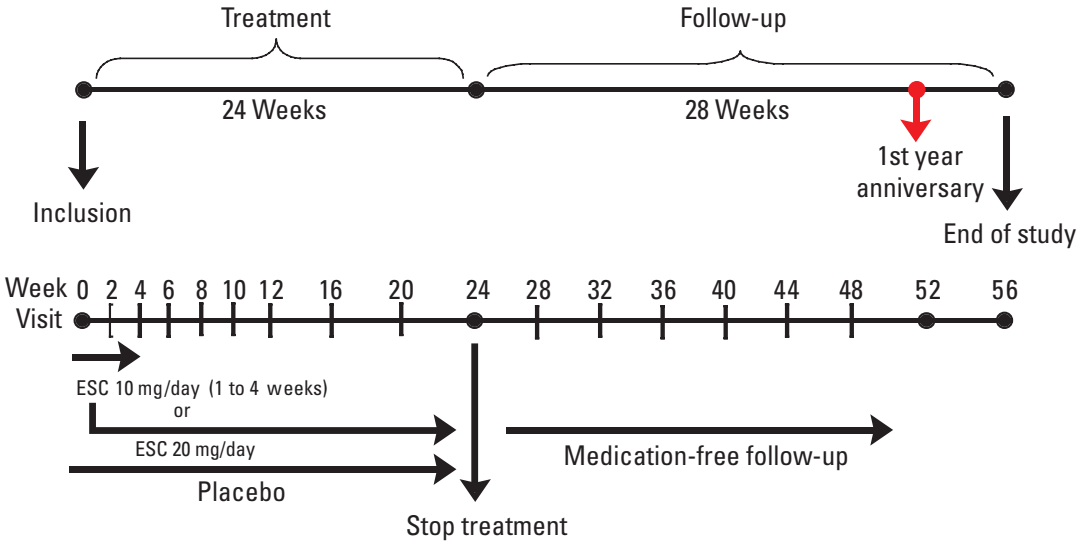
FIGURE 3.
Design of Study Currently Underway for Early Intervention with Escitalopram to Prevent PTSD



ESC=escitalopram.

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