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Pharmacological Secondary Prevention of PTSD in Youth: Challenges and Opportunities for Advancement

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Abstract

Child and adolescent posttraumatic stress disorder (PTSD) is associated with an increased risk for a number of deleterious mental and physical health outcomes that if untreated may persist throughout the life course. Efficacious interventions applied soon after trauma exposure have the potential to reduce or prevent the development of PTSD symptoms and their associated impact on behavior and physical health. We review extant research related to treatment-modifiable peritraumatic predictors of pediatric PTSD, which have informed an emerging field of pharmacologic secondary prevention (i.e., occurring shortly following trauma exposure) of PTSD. Challenges and opportunities for early posttrauma PTSD prevention are described. Finally, we offer new models for biologically informed integration of pharmacologic and psychosocial secondary prevention intervention strategies for children and adolescents.

As many as two thirds of youth experience at least one traumatic event by 16 years of age (Copeland, Keeler, Angold, & Costello, 2007). Responses to childhood traumatic experiences range from transient distress to development of chronic disorders such as posttraumatic stress disorder (PTSD; Copeland et al., 2007; Fairbank & Fairbank, 2009; Kilpatrick et al., 2003; Wilkinson & Carrion, in press). Early identification of youth at risk

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for PTSD and development of secondary preventive interventions (i.e., initiated shortly after a trauma) is critical to prevent psychological symptoms. Relative to adults, youth may be more sensitive to even transient symptoms and are less able to seek help (Berkowitz, Brymer, & Watson, 2011). In addition to event (i.e., type, frequency, severity of trauma) and environmental factors (i.e., family functioning, socioeconomic status, neighborhood stress, etc.), individual biology may play a key role in posttrauma adjustment (Yehuda & LeDoux, 2007). Biological research may inform both theories of PTSD and the development of pharmacologic interventions to prevent PTSD (Delahanty & Nugent, 2006; Langeland & Olff, 2008). Here we explore how contemporary understanding of neurobiological influences on the development of PTSD may inform secondary PTSD prevention; we describe extant research related to treatment-modifiable peritraumatic predictors of pediatric PTSD and pharmacologic secondary prevention of PTSD. Finally, we discuss next steps for the field including biologically informed integration of pharmacologic and psychosocial secondary prevention strategies for youth.

Acute Biology, Pharmacology, and Secondary Prevention

A few classes of drugs have shown preliminary efficacy in preventing PTSD when administered to patients shortly after a traumatic event. The majority of studies, however, have been conducted with adults and most have involved retrospective designs rather than randomized controlled trials (RCTs; see Table 1). Below, we review suspected biological mechanisms of examined medications and published tests of secondary prevention.

Research into the biology of PTSD has consistently demonstrated that PTSD is associated with elevated sympathetic nervous system (SNS) activity (Southwick, 1993). Elevated SNS activity assessed via heart rate (Kassam-Adams, Garcia-Espana, Fein, & Winston, 2005; Nugent, Christopher, & Delahanty, 2006) and urinary epinephrine and norepinephrine levels (Delahanty, Nugent, Christopher, & Walsh, 2005; Pervanidou et al., 2007) soon after a traumatic event have been positively associated with subsequent PTSD in youth. These findings are generally consistent with adult investigations that provided the impetus for an examination of the efficacy of propranolol, a β blocker, at preventing the development of PTSD in adults (Pitman et al., 2002). Propranolol acts to decrease sympathetic arousal, and administration in the acute (within hours) aftermath of trauma exposure is believed to reduce the likelihood of developing PTSD through its influence on arousal-based memory consolidation and reconsolidation (Debiec, Bush, & LeDoux, 2011; Debiec & LeDoux, 2006; Pitman & Delahanty, 2005). Propranolol's role in consolidation and reconsolidation of fear conditioning processes is supported by human studies of skin conductance level and subjective arousal (Grillon, Cordova, Morgan, Charney, & Davis, 2004), amygdala activity (Hurlmann et al., 2010), and laboratory learned startle-response (Soeter & Kindt, 2011).

Adult Secondary Prevention

Pitman and colleagues (Pitman et al., 2002) were the first to examine propranolol (40 mg four times daily [qid]) as a secondary prevention for PTSD in adults in a RCT. Although propranolol and placebo recipients did not differ in levels of PTSD symptoms at 1- or 3-months posttrauma, findings supported significant reductions in psychophysiological reactivity to script-driven imagery in the propranolol versus placebo group 3-months

posttrauma. A second open-label comparison of propranolol relative to no intervention reported decreased PTSD incidence in the propranolol condition (Vaiva et al., 2003). No differences, however, were observed in a third study that applied an alternative dosing strategy (see Table 1; Stein, Kerridge, Dimsdale, & Hoyt, 2007).

Child Secondary Prevention

We conducted an initial pilot investigation of the feasibility and acceptability of propranolol as an acute preventative intervention, randomizing pediatric trauma patients (aged 8–18 years) to receive either propranolol or placebo within 12 hours of hospital admission (Nugent et al., 2010). In addition to medical eligibility, participants were selected for risk for PTSD using a screener developed for pediatric hospital settings (Winston, Kassam-Adams, Garcia-Espana, Ittenbach, & Cnaan, 2003). Participants were randomized in a double-blind design (stratified by gender) to receive either propranolol (2.5 mg/kg/d, max 40 mg) or placebo twice daily for 10 days (based on Pitman et al., 2002). Although groups did not differ in PTSD symptoms after including covariates, a significant gender by treatment interaction was found. Specifically, whereas analyses revealed a suggestive pattern of decreased PTSD symptoms in boys who received propranolol, girls in the propranolol group reported more symptoms of PTSD than girls in the placebo group. Conclusions were limited by the small sample and uneven randomization of bereaved youth (all four bereaved youth were randomized to the propranolol condition); however, the differing effect related to gender requires further study. Although a thorough consideration of the literature regarding sex-related biologic differences and PTSD is outside the scope of this article, interested readers are directed to Olff, Langeland, Draijer, and Gersons (2007) for a review of this literature.

Glucocorticoids

Mechanism—Exposure to stress engages the hypothalamic–pituitary–adrenal (HPA) axis and induces adrenal synthesis and release of glucocorticoids, which led to the examination of HPA axis regulation/dysregulation in early adaptation to trauma. Animal models have suggested that blunted HPA-axis responses to stress are associated with increased PTSD-like reactions (Cohen et al., 2006), just as lower peritraumatic urinary cortisol has been found to predict the development of PTSD in adults (Delahanty, Raimonde, & Spoonster, 2000). Genetic investigations of PTSD in pediatric injury patients provide further support for the role of the glucocorticoid system in risk for PTSD in youth (Amstadter et al., 2011; Koenen et al., 2005). Given this evidence, glucocorticoid administration has been a widely explored method of pharmacointervention in PTSD. Glucocorticoids enhance extinction in chronic PTSD (Suris, North, Adinoff, Powell, & Greene, 2010), and high doses of hydrocortisone impair memory consolidation and recall (Het, Ramlow, & Wolf, 2005; Sauro, Jorgensen, & Pedlow, 2003). Some research has suggested that hydrocortisone administration may protect against stress induction of negative mood (Het & Wolf, 2007; Reuter, 2002; Soravia et al., 2006; Vasa et al., 2009). Yet another possibility is that hydrocortisone may variably impact threat- and affect-relevant behaviors such as avoidance of threat, particularly in temperamentally anxious or inhibited adults (Van Peer et al., 2007).

Adult secondary prevention—Preclinical research found that high doses of hydrocortisone administered to treat septic shock resulted in fewer PTSD symptoms (Schelling et al., 1999). One recent double-blind placebo-controlled pilot study compared hydrocortisone and placebo administration, initiated within 6 hours of the trauma, in 25 patients with acute stress disorder (ASD) symptoms (Zohar et al., 2011). Findings supported decreased symptoms of ASD and PTSD in the hydrocortisone intervention group. Similarly, a larger RCT examining the efficacy of a 10-day regimen of low-dose (20 mg, twice daily [bid]) hydrocortisone in seriously injured trauma patients found that hydrocortisone recipients reported significantly lower PTSD symptom severity at 1- and 3-month follow-up than placebo recipients (Delahanty et al., 2012).

Child secondary prevention—To our knowledge, no child studies have examined glucocorticoids for secondary prevention of PTSD. Preliminary studies suggest that children may not present with the same glucocorticoid response to traumatic stressors as adults (Delahanty et al., 2005; Kolaitis et al., 2011; Weems & Carrion, 2007). Whereas lower peritrauma cortisol levels have been associated with increased risk for PTSD in adults, in children, higher peritrauma cortisol levels have been related to subsequent PTSD risk (Delahanty & Nugent, 2006).

Opiates

Mechanism—In addition to the more widely studied noradrenergic and glucocorticoid systems, the opioid neurotransmitter system is also believed to play a role in the development of PTSD (Merenlender-Wagner, Dikshtein, & Yadid, 2009). Exogenously administered opiates are believed to activate μ -opioid receptors, exerting downstream influences on the acute stress response (McGaugh, Introini-Collison, & Nagahara, 1988; Morgan, Krystal, & Southwick, 2003). This is supported by evidence that opioid system variation associated with higher cortisol is also associated with PTSD (Hernandez-Avila, Wand, Luo, Gelernter, & Kranzler, 2003; Nugent, Lally, Brown, Knopik, & McGeary, 2011). Opiates may attenuate noradrenergic activation and dampen fear conditioning by serving to contain the HPA response (Good & Westbrook, 1995; McNally & Westbrook, 2003; Pitman, 1989).

Adult secondary prevention—To date, two nonrandomized studies have assessed the relationship between post trauma opiate administration and subsequent PTSD in adults. Bryant and colleagues examined the association between levels of morphine administration during the first week postinjury and 3-month PTSD symptoms (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2009). Relative to participants who did not meet criteria for PTSD at follow-up, participants with PTSD had received less morphine. Amount of morphine administration predicted PTSD symptoms after adjusting for injury severity, gender, age, and type of injury. In addition, retrospective analysis of injured U.S. troops from Iraq found that patients who received morphine in the early stages of their treatment following a traumatic event had a significantly lower rate of PTSD than soldiers who did not receive morphine (Holbrook, Galarneau, Dye, Quinn, & Dougherty, 2010).

Child secondary prevention—One of the first studies to examine the pharmacologic secondary prevention of PTSD using opiates was a retrospective chart review (Saxe et al., 2001). Children who were admitted to the hospital for acute burn injuries had a negative association between in-hospital morphine dose and 6-month PTSD symptoms. Partial support was also provided by another nonrandomized investigation of 48 youth recruited from the emergency department (Nixon et al., 2010). Although acute morphine administration was not associated with PTSD at 4-weeks posttrauma, it was associated with lower PTSD symptoms at 6 months as well as with a reduction of symptoms between 1-month and 6-month follow-ups. Of note, youth in the Nixon et al. study received a lower average dose (0.17 mg/kg/d) than youth in the Saxe et al. investigation (who received an average of 0.80 mg/kg/d). Stoddard and colleagues (2009) also examined the association between PTSD symptoms at 3- and 6-months posttrauma and acute morphine administration during medical care in 70 very young (12- to 48-month-old) burned children. Findings supported a significant protective effect of morphine dose on subsequent PTSD symptoms, particularly symptoms of arousal.

Antidepressants

The rationale for the use of antidepressant medication in secondary prevention of PTSD in adults stems primarily from evidence supporting the use of antidepressants for treatment of depression in adult trauma victims. There is limited information suggesting a neurophysiologic rationale for their use for secondary prevention.

Child secondary prevention—To date, two studies of burned youth have examined antidepressant administration in treatment of ASD. Specifically, Robert, Blakeney, Villarreal, Rosenberg, and Meyer (1999) performed a 7-day comparison of the antidepressant imipramine versus chloral hydrate (a sleep medication) in pediatric burn victims and found that low-dose imipramine resulted in a significant reduction in ASD symptoms. The research group later examined ASD symptoms in 60 youth (ages 4–18 years) randomized to a one-week double-blind course of the antidepressants imipramine or fluoxetine versus placebo (Robert et al., 2008). A 50% reduction in ASD symptoms was found in 55% of placebo participants, 60% of imipramine participants, and 72% of fluoxetine participants. Stoddard and colleagues used a double-blind placebo-controlled design to assess 26 children aged 6–20 years who had received 25–150 mg of the antidepressant sertraline/day or placebo following presentation with severe burns (Stoddard et al., 2011). Results revealed no significant difference in child-reported symptoms of PTSD over time compared to baseline; however, subjects treated with sertraline exhibited a larger decrease in parent-reported symptoms at 8-, 12-, and 24-week follow-ups compared to subjects administered placebo. A recent review of published investigations has not supported the efficacy of selective serotonin reuptake inhibitor/selective serotonin-norepinephrine reuptake inhibitor (SSRI/SS-NRI) treatment for child PTSD (Strawn, Keeshin, DelBello, Geraciotti, & Putnam, 2010).

Existing Interventions: Highlighting Challenges And Opportunities

Although a significant minority of trauma victims develops PTSD, those who develop PTSD experience debilitating symptoms and comorbidities. Therefore, it is critical to try to identify at-risk individuals so that limited resources can be efficiently and cost-effectively administered. As we outline below, research aimed at developing and testing acute interventions should be designed with attention to unique considerations.

First, research should be developmentally tailored. Although adult studies may be used to inform child interventions, it is important to recognize that environmental and biological influences may differ in children relative to adults. For instance, as described elsewhere (Delahanty & Nugent, 2006; Delahanty et al., 2005), children and adults may differ with respect to early biological predictors of PTSD, and as such may differ in their responses to early pharmacological prevention.

Second, research should test for gender differences. Biological risk factors differ substantially in boys and girls (Delahanty & Nugent, 2006; Olff et al., 2007), particularly during puberty (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). Further, our finding that propranolol was associated with more PTSD symptoms in girls but marginally fewer in boys suggests that early pharmacologic intervention approaches may differ by gender (Nugent et al., 2006).

Third, research should be informed by the risk profile of the sample. Recognizing that not all individuals at risk for PTSD show the same biological and behavioral responses, future pharmacologic studies should work to identify ways to match or tailor interventions to the unique characteristics of the recipient's environmental, psychological, and neurobiological response. An additional important consideration involves the type of trauma experienced, as differing types of trauma (interpersonal, unintentional injury, etc.) are associated with differing risk for PTSD and may be related to differential efficacy of secondary interventions. To date, nearly all biological studies of PTSD have examined group differences in early risk factors, potentially masking subgroup differences that could be important for tailoring interventions.

Fourth, research should be timed in a manner that is consistent with the recognized mechanism of action. For example, if a medication is believed to exert its effects during initial consolidation of a traumatic memory, the regimen would need to be initiated during that acute window of memory formation. If, instead, the mechanism is believed to be related to early reconsolidation or avoidance, an intervention could be initiated within hours (possibly even days) of the trauma. Similarly, duration of the regimen should be matched to the proposed mechanism. For example, medications believed to be important to reconsolidation or avoidance might be most efficacious if the regimen continues several weeks posttrauma.

Finally, particularly in research with youth, studies should consider the role of family in posttraumatic adjustment. We have previously demonstrated substantial effects of parent symptoms on subsequent child PTSD and further have found that the predictive utility of early biological risk factors is moderated by parent response (Nugent, Ostrowski,

Christopher, & Delahanty, 2007). It is unlikely that a purely biologically mediated intervention will affect the influence of environmental factors such as family. The complexity of the interaction of an individual child's biological profile with family functioning may require a more comprehensive preintervention assessment of the patient and family to better inform intervention content.

As research works toward secondary prevention efforts that consider these five key guidelines for child secondary PTSD prevention, new paradigms for treatment interventions that integrate the important transactional influences of biology and environment on development of PTSD should be developed.

New Paradigms for Early Intervention

Moving forward, early intervention research efforts should benefit from attention to the aforementioned issues. Further, it will be important to recognize that specific pharmacologic approaches may not comprehensively address all PTSD symptoms. Although medications such as propranolol may serve to target fear-conditioning influences on PTSD development, additional factors such as family environment or cognitions about the traumatic event are critical influences on the development and maintenance of symptoms. Given the complexity of PTSD, multiple approaches may be needed to prevent PTSD in trauma-exposed youth.

Psychosocial Intervention Models

Several studies in adults have demonstrated the effectiveness of cognitive-behavioral therapy and Prolonged Exposure (PE) interventions for symptomatic adults in the early posttrauma period (Agorastos, Marmar, & Otte, 2011). The majority of early psychosocial preventative interventions for youth, however, has little empirical evidence and has been described as "evidence informed" (Berkowitz et al., 2011). Four psychosocial interventions have been tested as RCTs (Berkowitz et al., 2011; Kassam-Adams, et al., 2011; Kenardy, Thompson, Le Brocque, & Olsson, 2008; Zehnder, Meuli, & Landolt, 2010). Brief interventions (one to two sessions) and informational interventions have shown no significant differences related to PTSD symptoms (Kassam-Adams, et al., 2011; Kenardy et al., 2008; Zehnder et al., 2010), although these studies have observed intervention-related reductions in anxiety in children ages 7–15 years (Kenardy, et al., 2008) and in depressive and behavioral problems in preadolescent youth (Zehnder et al., 2010). Our group recently published promising findings for the Child and Family Traumatic Stress Intervention (CFTSI), a four-to-six session secondary prevention intervention designed to intervene with children aged 8 years and older and their adult caregivers within 30 days of experiencing a traumatic event (Berkowitz, Stover, & Marans, 2011). Youth were randomized to either CFTSI ($n = 53$) or to a four-session psychoeducational and supportive intervention ($n = 53$). Participants were recruited from a pediatric emergency department, a forensic sexual abuse program, and a police department's victim services department following a wide range of traumatic events. Youth who participated in CFTSI were 65% less likely to develop chronic PTSD at the 3-month follow-up than youth who participated in the comparison condition. The CFTSI recipients also reported significantly fewer posttraumatic and anxiety symptoms posttreatment and remained lower at the 3-month follow-up. Despite these promising findings, psychosocial intervention as a means to secondary prevention of PTSD remains in

its early stages of development and implementation. Future RCTs involving an integration of both pharmacologic and psychosocial intervention may prove more effective in secondary prevention of PTSD.

Integrating Pharmacologic and Psychosocial Intervention

There has been increasing interest in the synergistic use of pharmacology combined with psychosocial interventions in the treatment of PTSD. For instance, pairing D-cycloserine with PE to increase the efficacy of PE has shown promise (Choi, Rothbaum, Gerardi, & Ressler, 2010; Cukor, Spitalnick, Difede, Rizzo, & Rothbaum, 2009). Such combination pharmacologic–psychosocial interventions may also be efficacious at preventing the development of PTSD. For instance, initial propranolol administration has been found to reduce initial conditioned fear and initial hyperarousal associated with PTSD, whereas CFTSI (although not efficacious at reducing hyperarousal) has been associated with decreases in intrusive/avoidant thoughts and behaviors. It is possible that CFTSI may provide familial support to enhance propranolol's efficacy. Interestingly, there is evidence that early parent functioning may be more important to later posttraumatic stress symptoms for girls than for boys (Ostrowski, Christopher, & Delahanty, 2006). Thus, medication in youth may be most helpful for girls if they also incorporate interventions with caregivers or with the child–parent relationship. Taken collectively, findings suggest that combination psychosocial–pharmacological intervention approaches may be more efficacious than either approach alone.

Summary And Conclusions

In sum, the field of secondary prevention of PTSD in youth remains in its infancy. Future advances in the secondary prevention of PTSD in youth will be strengthened by the acknowledgment that interventions should be developmentally tailored, anticipate gender-specific effects, be informed by individual risk profiles, be timed in a manner that is consistent with the believed mechanism of action, and should incorporate programming to address the critical role of family and severity of injury in child posttraumatic response. We propose that research efforts integrating psychosocial strategies with pharmacologic prevention may be especially well suited to youth. Furthermore, identification of key risk profiles will help direct clinicians in determining which methods of secondary intervention will be most appropriate and efficacious. Such advances should enhance the success of secondary prevention of PTSD in children and adolescents and greatly improve posttrauma outcome in this vulnerable population.

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Table 1

Randomized Controlled Trials of PTSD Secondary Prevention

Investigators	Sample	N	% Male	Medication	Dose	Initiation	Duration	Findings
Adult Studies								
Pitman et al., 2002	ED patients	41	49	Propranolol vs placebo	40 mg qid	~ 4 h posttrauma	10 d, 9-d taper	Propranolol: Reduced psychophysiological response to script-driven imagery
Zohar et al., 2011	Acute stress patients	17	53	Hydrocortisone vs placebo	100–140 mg	Within 6 h posttrauma	Single intravenous bolus	Hydrocortisone: Attenuated ASD symptoms and subsequent PTSD
Stein et al., 2007	Trauma center injury patients	48	54	Propranolol vs gabapentin vs placebo	Propranolol: Up to 40 mg tid; gabapentin: up to 400 mg tid	Within 48 h of admit	14 d	No significant differences for depressive or PTSS reduction
Youth Studies								
Nugent et al., 2010	Pediatric trauma patients	29	52	Propranolol vs placebo	2.5 mg/kg/d (max 40 mg) bid	Within 12 h of admit	10 d, 5-d taper	No medication differences in combined sample
Stoddard et al., 2011	Child burn patients (6–20 years old)	26	65	Sertraline vs placebo	25–150 mg/d	Unclear	24 wk	No significant difference in change in child-reported PTSD symptoms; greater decrease in parent-reported symptoms over 8-, 12-, and 24-weeks in sertraline

Note. PTSD = Posttraumatic stress disorder; ED = emergency department; ASD = acute stress disorder; PTSS = posttraumatic stress symptoms; mg = milligram; kg = kilogram; qid = four times a day; tid = three times a day; bid = twice daily.