

Pilot Study of Secondary Prevention of Posttraumatic Stress Disorder with Propranolol

Roger K. Pitman, Kathy M. Sanders, Randall M. Zusman, Anna R. Healy, Farah Cheema, Natasha B. Lasko, Larry Cahill, and Scott P. Orr

Background: *Preclinical considerations suggest that treatment with a β -adrenergic blocker following an acute psychologically traumatic event may reduce subsequent posttraumatic stress disorder (PTSD) symptoms. This pilot study addressed this hypothesis.*

Methods: *Patients were randomized to begin, within 6 hours of the event, a 10-day course of double-blind propranolol ($n = 18$) versus placebo ($n = 23$) 40 mg four times daily.*

Results: *The mean (SD) 1-month Clinician-Administered PTSD Scale (CAPS) score of 11 propranolol completers was 27.6 (15.7), with one outlier 5.2 SDs above the others' mean, and of 20 placebo completers, 35.5 (21.5), $t = 1.1$, $df = 29$, $p = .15$. Two propranolol patients' scores fell above, and nine below, the placebo group's median, $p = .03$ (sign test). Zero of eight propranolol, but six of 14 placebo, patients were physiologic responders during script-driven imagery of the traumatic event when tested 3 months afterward, $p = .04$ (all p values one-tailed).*

Conclusions: *These pilot results suggest that acute, post-trauma propranolol may have a preventive effect on subsequent PTSD. Biol Psychiatry 2002;51:189–142*
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Introduction

Pharmacologic secondary prevention of posttraumatic stress disorder (PTSD) (i.e., intervening after a traumatic event to forestall PTSD's development), is a topic of current medical interest that has received little investiga-

tion (Larkin 1999). Preclinical research has shown that epinephrine, exogenously administered or endogenously released, after a learning task strengthens memory consolidation and fear conditioning. This seems to be an adaptive mechanism whereby the significance of an experience facilitates its remembrance. The locus of this effect seems to be the amygdala (McGaugh 1990). The β -adrenergic blocker propranolol, which crosses the blood-brain barrier, administered pre- (Rooszendaal et al 1997) or post- (Cahill et al 2000) training, abolishes this effect in animals and humans (Cahill et al 1994). The β -adrenergic blocker nadolol, which does not cross the blood-brain barrier, does not (van Stegeren et al 1998).

We have postulated that an excess of epinephrine release at the time of a psychologically traumatic event leads to overly strong emotional memory and fear conditioning that subsequently manifest themselves as PTSD symptoms (Pitman 1989). If this theory is correct, then administering propranolol soon enough after a traumatic event to block β -adrenergic receptors might have a preventive effect. We report here the results of a double-blind, placebo-controlled pilot study addressing this hypothesis.

Methods and Materials

Subjects

We recruited 41 Emergency Department (ED) patients who (a) had just experienced a traumatic event that met the DSM-IV PTSD A.1 (stressor) and A.2 (response) criteria; (b) had a heart rate (HR) of 80 beats per minute (BPM) or greater at the time of ED presentation; (c) were without serious physical injury, systolic blood pressure under 100 mm Hg, substance intoxication, pregnancy or lifetime history of congestive heart failure, heart block or bronchial asthma; (d) upon mental status examination were found competent to understand the purpose of the study and the nature of the procedures; and (e) gave written informed consent after the procedures had been fully explained.

Ethical Safeguards

Additional ethical safeguards for this placebo-controlled study were as follows: (a) Subjects received supportive counseling

From the Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (RKP, KMS, RMZ, ARH, FC, NBL, SPO), the VA Medical Center Research Service, Manchester, New Hampshire (NBL, SPO), and the Center for the Neurobiology of Learning and Memory, University of California, Irvine, California (LC).

Address reprint requests to Roger K. Pitman, PTSD Research Laboratory, Massachusetts General Hospital-East, Bldg. 149, 13th Street, Charlestown Massachusetts 02129.

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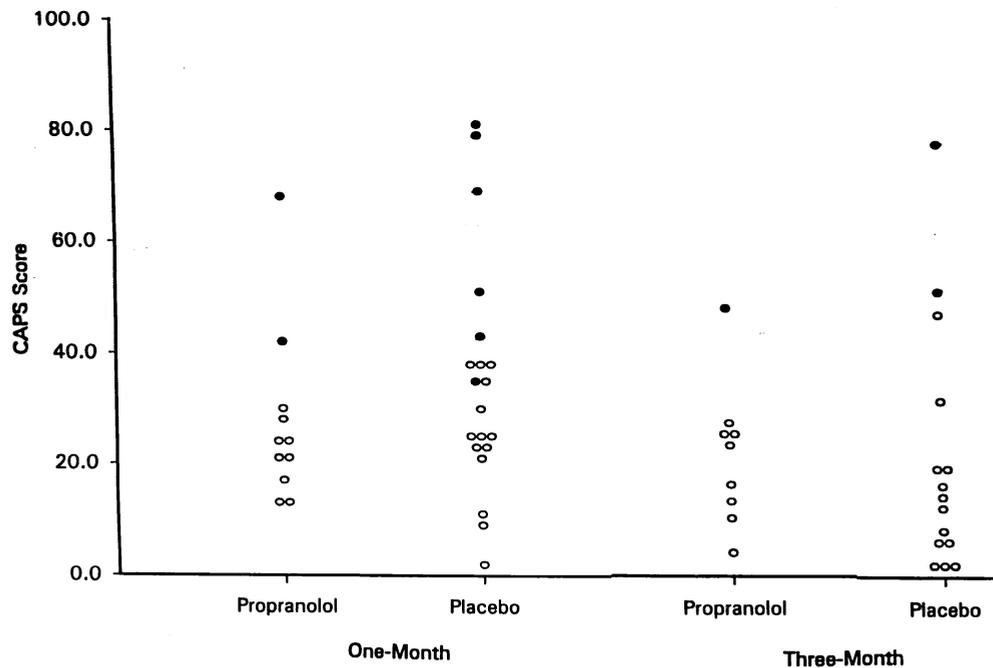


Figure 1. Clinician-administered posttraumatic stress disorder scale scores. Black circles indicate patients who met categorical DSM-IV criteria for posttraumatic stress disorder.

from the research nurse as appropriate during the course of their participation. (b) The research nurse was in regular contact with participants regarding the occurrence of medication side effects or serious adverse events (none of the latter occurred to our knowledge). (c) Subjects were advised that participation in the study did not rule out their receiving other psychiatric or clinical psychological help. (d) Subjects were initially informed and reminded during the course of the study that they were free to withdraw their participation at any time without penalty.

Study Medication

The first 40 mg oral dose of propranolol or placebo was administered as soon as possible, but no longer than 6 hours, after the traumatic event. Approximately 1 hour later, patients were medically cleared to leave the ED and instructed to continue the medication four times daily as tolerated for 10 days, followed by a 9-day taper period.

Outcome Assessment

One and three months later, patients returned for psychometric assessment with the Clinician-Administered PTSD scale (CAPS; Blake et al 1995), which was administered by a highly experienced, doctoral-level psychologist whose reliability for total CAPS score, as measured against another interviewer, is inter-rater = .99, test-retest = .94 (intraclass correlation coefficients).

After the 3-month CAPS assessment, patients underwent a script-driven psychophysiological imagery procedure that has been shown to discriminate subjects with and without PTSD (Pitman et al 1987). They listened to tape-recorded scripts portraying, in their own words, the traumatic event that had

brought them to the ED, and then imagined this event for 30 sec., while or at the same time as HR, skin conductance (SC) and left lateral frontalis and left corrugator electromyograms (EMGs) were measured. From the mean level during the imagery period, the mean level of each physiologic variable during the preceding baseline period was subtracted to yield HR, SC and EMG responses.

Results

Pre-Medication Variables

Of 18 patients randomized to propranolol, eight (44%) were males and 13 (72%) had a motor vehicle accident (MVA) event. Of 23 patients randomized to placebo, 12 (52%) were males and 16 (70%) had a MVA event. Propranolol versus placebo group means (SDs) included: age (years), 34.3 (11.1) versus 34.3 (10.2); self-rated event severity (0–10 scale), 5.3 (1.5) versus 5.6 (2.2); self-rated response intensity (0–10 scale), 8.0 (1.7) versus 7.5 (2.8); time between traumatic event and first dose of study medication (min), 255 (124) versus 246 (120); HR at ED arrival (BPM), 92.7 (9.5) versus 95.1 (12.1); HR at ED departure (BPM), 80.9 (9.9) versus 82.7 (12.8). None of these group differences approached statistical significance.

Clinician-Administered PTSD Scale

Figure 1 presents the 1- and 3-month propranolol and placebo completers' CAPS scores. Eleven (61%) propranol-

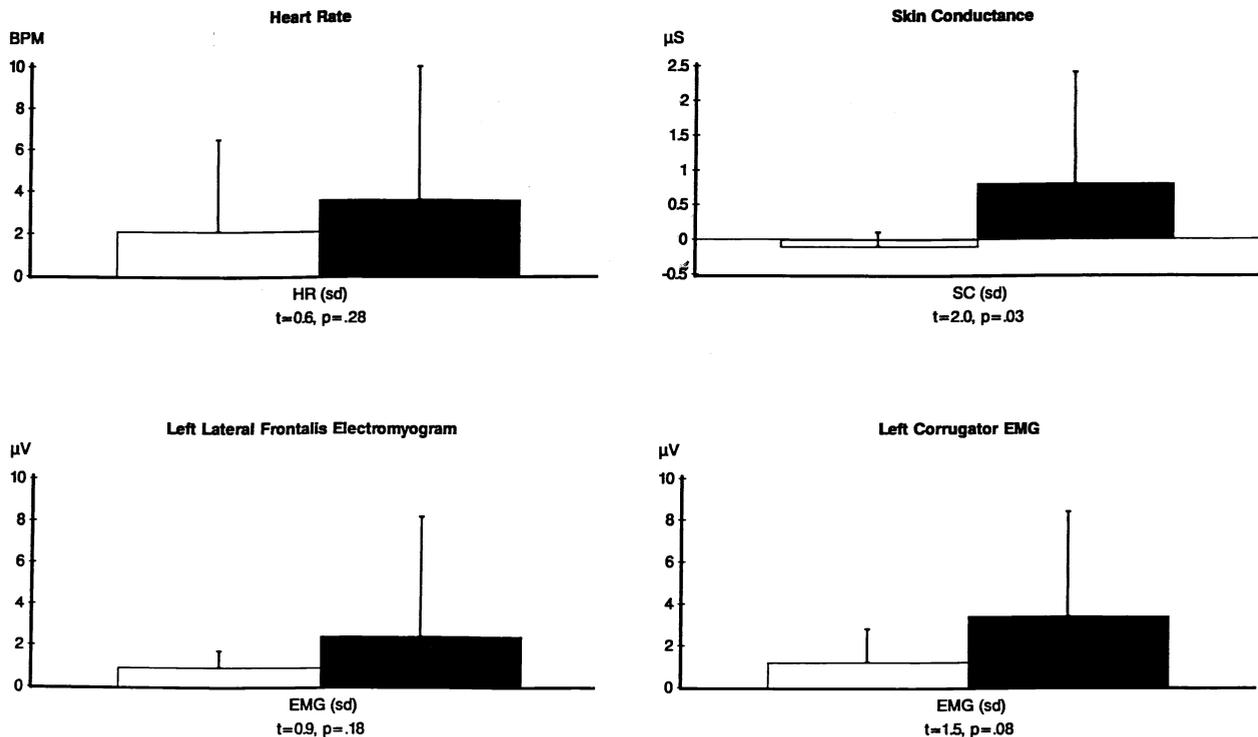


Figure 2. Physiologic responses during personal script-driven imagery of the traumatic event that occurred 3 months earlier. White bars indicate propranolol ($n = 8$) and black bars placebo ($n = 14$) patients (frontalis electromyogram data missing in two patients). Degrees of freedom: HR 20, SC 13.5*, frontalis electromyogram 14.2*, corrugator electromyogram 17.3*. Asterisk designates t test for unequal variances. All p values are one-tailed.

olol and 20 (87%) placebo patients returned for the 1-month assessment (two-tailed $p = .08$; all 2×2 tables analyzed by Fisher's Exact Test). Group mean (SD) 1-month CAPS scores were: propranolol 27.6 (15.7), placebo 35.5 (21.5), $t = 1.1$, $df = 29$, one-tailed $p = .15$. These parametric results were heavily influenced by a propranolol outlier whose CAPS score was 5.2 SDs above the other propranolol completers' mean. A nonparametric sign test of the number of propranolol subjects whose 1-month CAPS scores were above (two) versus below (nine) the placebo group's median of 32.5 yielded $p = .03$, one-tailed. Nine (50%) propranolol and 15 (65%) placebo ($p = .36$, two-tailed) patients returned for the 3-month assessment. Group mean CAPS scores (SD) were: propranolol 21.1 (12.5), placebo 20.5 (21.7), $df = 22$, $t = -.01$, $p = ns$.

Categorical PTSD Outcome

At 1 month, with the outlier included, the PTSD rate was 6/20 (30%) in the placebo completers and 2/11 (18%) in the propranolol completers ($p = .39$, one-tailed). With the outlier excluded, the PTSD rate was 6/20 (30%) in the placebo and 1/10 (10%) in the propranolol completers

($p = .19$, one-tailed). At 3 months, one (11%) of the remaining 11 propranolol patients (the outlier) and two (13%) of the remaining 15 placebo patients met DSM-IV criteria for chronic PTSD (with outlier included, $p = .62$; with outlier excluded, $p = .35$, both one-tailed).

Psychophysiological Assessment

Eight (44%) propranolol and 14 (61%) placebo ($p = .36$, two-tailed) patients returned for psychophysiological assessment. The propranolol and placebo group mean (SD) responses appear in Figure 2. An *a priori* discriminant function derived from the HR, SC and corrugator EMG responses during personal traumatic imagery of 33 individuals with PTSD and 35 individuals without PTSD previously studied in our laboratory (Pitman et al 1999) classified zero (0%) of the eight propranolol versus six (43%) of the 14 placebo patients as physiologic responders ($p = .04$, one-tailed; because frontalis EMG data were missing from two patients for technical reasons, this variable was not included in the discriminant function). The discriminant function yielded only a 4% chance that the CAPS outlier in the propranolol group would be classified as PTSD.

Discussion

The results of this pilot study support the clinical feasibility of testing the hypothesis that a course of propranolol begun shortly following an acute traumatic event is efficacious in reducing PTSD symptoms 1 month later. The pilot results also offer initial promise for this hypothesis, although conclusions must await adequately powered studies with larger samples. The observation that HR decrease from pre- to poststudy medication in the ED was comparable in the propranolol (11.8 BPM) versus placebo (12.4 BPM) groups suggests that the initial 40 mg dose of propranolol was insufficient to fully attenuate patients' acute posttraumatic hyperadrenergic states. Because the first 6 hours may represent a window of opportunity (Shadmehr and Holcomb 1997), this may have biased against our finding an effect of propranolol on the PTSD outcome measures. Future studies should consider using larger initial doses.

Three-month CAPS scores did not differ in the propranolol and placebo groups. Rather, it seems that most patients' symptoms settled to nonclinical levels. However, the psychophysiological testing results suggest that the posttrauma course of propranolol reduced patient's reactivity on exposure to internal cues (i.e., mental imagery) that symbolized or resembled the traumatic event that originally brought them to the ED (DSM-IV PTSD criterion B.5, American Psychiatric Association 1994, p. 428) when this reactivity was measured 3 months later. These pilot results are analogous to the ability of posttraining propranolol to reduce animals' retention of a conditioned fear response acquired in the laboratory (Cahill et al 2000).

This pilot study has several limitations, including small initial sample sizes made even smaller by attrition over the stages of the study, differential attrition in the propranolol group, possible patient noncompliance with study medication (which was not formally monitored), possible differential nurse attention to propranolol subjects (who were more likely to have side effects) and sample sizes too small to address potentially confounding factors such as

comorbidity and concurrent other medication use or treatment. These factors will need to be addressed in further, larger studies.

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