

Propranolol, Other Drugs Eyed to Block PTSD

Idea is that blocking β -adrenergic receptors might tone down consolidation of emotional memories.

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Over the next several years, victims of car accidents, crimes, or other traumas who are treated at Boston's Massachusetts General Hospital will be offered a commonly used heart drug—the β -adrenergic blocker propranolol—to potentially help lessen the intensity and future impact of traumatic memories.

Patients who participate in this study will be part of a wave of new drug trials aimed at intervening early to alter memory processes and prevent posttraumatic stress disorder (PTSD). Other studies are planned to aim at intervening later to treat PTSD by effecting memory “reconsolidation,” the process by which memories that have been reactivated are then restored.

As neurobiologists press on with research to better understand the mechanisms and processes involved in acquiring and storing traumatic memories, clinical investigators say they cannot wait to field-test propranolol and other commonly available drugs, some of which appear to target specific mechanisms of action in fear memory.

And some physicians may not even be waiting for study results. According to anecdotal reports, propranolol is already being used off label sporadically in the immediate wake of traumatic experiences.

Possible Clinical Benefits

“There’s a real good possibility [we’ll soon be using] more specific medications than we have now that will help us deal with the effects of psychological trauma [on the brain],” said Dennis S. Charney, M.D., dean of research at Mount Sinai School of Medicine, New York.

“We’ll likely be able to use medication to facilitate fear extinction, to reduce the consolidation of fear memories, and in a rational way, to use medications to augment the effects of psychotherapy,” he said.

The study at Massachusetts General builds on a pilot study, published in 2002, that suggested that posttrauma administration of propranolol in the emergency room may have a “preventive effect” on subsequent PTSD. (See sidebar.)

Harvard/NIMH Study Design

Roger Pitman, M.D., who led the pilot study and has a \$2.5 million grant from the National Institutes of Mental Health to conduct the larger double-blind randomized study, hopes to recruit at least 100 patients who have both experienced a traumatic event and present with tachycardia of at least 80 beats/min.

According to Dr. Pitman, most of the published and soon to be published studies addressing the issue of tachycardia as a predictor of PTSD “have been positive.”

Patients in his study will be randomized to receive, within 6 hours of the event, a 10-day course of placebo or propranolol followed by a 9-day taper period, said Dr.

Pitman, professor of psychiatry at Harvard Medical School, Boston.

Propranolol is commonly used to treat high blood pressure and for other cardiovascular purposes. It is also prescribed, albeit less frequently, as an anti-anxiety therapy adjunct for people with public speaking anxieties, fear of flying, and other phobias. It is the only β -blocker that can cross the blood-brain barrier, Dr. Pitman said.

Possible Mechanism of Action

Dr. Pitman latched onto the idea of testing the drug for PTSD prevention 10 years ago, when Larry Cahill, Ph.D., of the Center for the Neurobiology of Learning and Memory at the University of California, Irvine, reported that in a small study of healthy people, the drug significantly impaired memory of an emotionally arousing story but did not affect memory of an emotionally neutral story (*Nature* 1994;371:702-4).

The findings backed a long-standing hypothesis that enhanced memory associated with emotional experiences results from activation of the β -adrenergic stress hormone systems, particularly in the amygdala. If β -adrenergic receptors are blocked, the theory goes, the consolidation of emotional memories—the formation and storage of long-term emotional memories—can be toned down. As some neurobiologists like to describe it, “over-consolidation”—and overly strong emotional memories—can be prevented.

“The study bridged the gap,” Dr. Cahill said. “It looked like what we were seeing in animals would hold up in humans.”

Studying SSRIs for PTSD Prevention

Other physicians have their eyes on the use of selective serotonin reuptake inhibitors (SSRIs) for PTSD prevention.

At Massachusetts General, Mark Pollack, M.D., is testing the SSRI Lexapro (escitalopram) “at the next potential point of intervention”—in patients who, within a few weeks after trauma, are experiencing acute stress symptoms but do not meet the full criteria for PTSD.

The possible mechanisms of action of the SSRIs in such cases are not all clear, but the hope is that the drugs will help interrupt the cycle of increased arousal and anxiety that may predispose to full-blown PTSD, said Dr. Pollack, director of the hospital's Anxiety and Traumatic Stress Disorders Program. SSRIs are often used (with moderate success) today to treat syndromal PTSD.

Physicians at the Center for the Study of Traumatic Stress at the Uniformed Services University of the Health Sciences in Bethesda, Md., have started a similar study, administering an SSRI to car accident victims days to several weeks after the event. Robert Ursano, M.D., who chairs the department of psychiatry at the university, is optimistic enough about these and other studies that he says that “PTSD may be the first psychiatric illness that we’ll be able to prevent.”

Therapeutic Window of Opportunity

A major question faced by investigators concerns the timing of the memory consolidation processes. “We don’t know what our window of opportunity is,” Dr. Pitman said. “In the most pessimistic estimate, it takes 30 minutes. And it takes at least 30 minutes for propranolol to be absorbed. Some data suggest, though, that the process may take 8 hours.”

Some physicians think that given these uncertainties—as well as lingering questions about who is most at risk for developing PTSD, and limitations in reaching many people early after trauma—it may be more feasible to intervene later and to work on memories that already have formed.

The idea is to reactivate or retrieve the memory and, while it is briefly vulnerable, attempt to weaken it before the memory is restored.

At the October meeting of the Society of Neuroscience, investigators from the Center for Neural Science at New York University presented preliminary findings from animal and human studies that suggested that propranolol at least partly disrupts the “reconsolidation” of fear memories, via the amygdala, making the memories significantly weaker. One of the studies, led by Jacek Debiec, M.D., of New York University, New York, was published in the October issue of *Neuroscience* (2004;129:267-72).

Other Research Ventures

NYU physicians have begun working with others at the multi-institutional Center for the Neuroscience of Fear and Anxiety on testing whether propranolol helps PTSD patients who take it after recalling traumatic experiences.

Dr. Pitman also is planning a study with Karim Nader, Ph.D., a neuroscientist at McGill University in Montreal, in which they will invoke traumatic memories of PTSD patients and measure the ability of propranolol to reduce the subsequent strength of the memories.

The notion of “reconsolidation” is still controversial among neuroscientists. It’s unclear what exactly happens to memories after they’re reawakened, and whether attempts to block reconsolidation processes actually block memory restorage or make memories harder to retrieve.

Ethical questions have been raised, but Dr. Nader maintains that the term “therapeutic forgetting”—a phrase that has helped fuel some of the ethical debate—is misleading.

“Memory erasure isn’t what we’re aiming for. We know that with reactivation of a memory the mechanisms mediating the intensity of the memory will also undergo reconsolidation, and that’s what we’re targeting,” he said. “We’re trying to affect the intensity of the memory ... to turn down the volume.”

Current Clinical Use

In the meantime, it is unclear how many physicians have recommended drugs such as propranolol to try to prevent posttrauma suffering.

Physicians contacted by this newspaper said they’re unaware of propranolol being used off label for this purpose. Dr. Pitman, however, said that while he does not condone it, “it’s happening ... I’ve heard anecdotal reports.”

“I hope we’ll hear more about propranolol, especially with the war, with terrorism,” Dr. Debiec said. “We know the drug, we know it’s safe.” ■

Small Pilot Studies Serve as Backdrop

Dr. Pitman’s initial study of propranolol is one of two small pilot studies that have looked at treatment with the drug shortly after a traumatic event.

Forty-one patients were randomized in the emergency department at Massachusetts General Hospital to begin—within 6 hours of a traumatic event—a 10-day course of propranolol (40 mg four times daily) or placebo. Eighteen of the 41 received propranolol.

Patients in the double-blind study were instructed to return 1 and 3 months later for assessment with the Clinician-Administered PTSD Scale (CAPS). At the 3-month follow-up, investigators also measured patients’ physiologic responses during script-driven imagery of the traumatic event.

At 1 month, the PTSD rate was 30% in the placebo group (6 of 20 patients who returned for follow-up) and 18% (2 of 11 who returned) in the propranolol group.

At 3 months, the CAPS scores did not differ. However, the psychophysiology testing results suggested that propranolol had an impact. None of the 8

propranolol patients who participated, but 6 of the 14 participating placebo patients, were physiologic responders, reported Dr. Pitman and his associates (*Biol. Psychiatry* 2002;51:189-92).

The second study was a nonrandomized study of patients who were treated in the emergency departments of two hospitals in France. Eleven patients received propranolol for 7 days (40 mg three times daily), with the first dose administered 2-20 hours after the trauma and with a taper period of 8-12 days. They were compared with 8 patients who refused propranolol but agreed to participate.

PTSD rates, as well as PTSD symptom scores, were higher in the patients who refused the drug (3 of 8) than in patients who took it (1 of 11), reported Guillaume Vaiva, M.D., of the University of Lille (France), and his associates (*Biol. Psychiatry* 2003;54:947-9).

“The French study showed a significant reduction of PTSD symptoms—we only found a significant trend,” Dr. Pitman said.

Patients in both studies had tachycardia.