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Tana M. Peterman
Ohio Northern University

Alison L. Huet
Ohio Northern University

Sarah E. Drake
Ohio Northern University

Jamie L. Drees
Ohio Northern University

Robert D. Raiff
Ohio Northern University

See next page for additional authors

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The Use of Propranolol in the Treatment of Post-traumatic Stress Disorder

Tana M. Peterman, fourth-year pharmacy major from Jacksonville, N.C., Alison L. Huet, fourth-year pharmacy major from Pittsburgh, Pa. Sarah E. Drake, fourth-year pharmacy major from Fairfield, Ohio, Jamie L. Drees, fifth-year pharmacy major from Canal Winchester, Ohio, Robert D. Raiff, fifth-year pharmacy major from Westlake, Ohio; B. Shane Martin, PharmD

Abstract

This article examines the rising issue of post-traumatic stress disorder (PTSD) and possible treatment options. PTSD is a behavioral disorder resulting from memory formation and association with a traumatic event. A search of the published literature reveals several positive studies and case reports suggesting that propranolol, a beta adrenergic receptor antagonist, may be useful for both treatment and prevention of PTSD. Additionally, current studies are being completed in different population groups to determine the overall effectiveness and mechanism by which propranolol is able to provide relief from certain symptoms common to the disorder. This article discusses the medical evidence and possible treatment role of propranolol for patients suffering from PTSD.

Background

Post-traumatic stress disorder (PTSD) is defined by DSM-IV as a traumatic incident in which a person experiences a life-threatening event that involves extreme fear that is persistently re-experienced.[1] PTSD is particularly seen in military veterans, including 29 percent of combat veterans and 78 percent of prisoners of war. Besides military-related causes, automobile accidents account for 56 percent of cases, and personal assault accounts for 35 percent of PTSD cases.[2] In order to be diagnosed with PTSD, a patient must be experiencing symptomology greater than one month after the traumatic incident.[1] Clinical characteristics of PTSD include re-experiencing symptoms, avoidance of certain situations, and hyperarousal symptoms along with the possibility of other miscellaneous symptoms (Table 1).

These characteristics can cause social, occupational and relational dysfunction. PTSD can be classified based on the occurrence and duration of these characteristics. If the patient experiences symptoms for less than three months after the incident, it is considered acute PTSD. The experiencing of symptoms greater than three months classifies patients as having chronic PTSD. Finally, a patient who does not experience these indicators until six months after the event are considered to have delay-onset PTSD.[1]

Table 1: Classic PTSD Characteristics

Classification	Examples
Re-experiencing Symptoms	Flashbacks, nightmares, frightening thoughts
Avoidance Symptoms	Staying away from places, events and objects that are reminders of traumatic event
Hyperarousal Symptoms	Easily startled, feeling tense, difficulty sleeping, angry outbursts
Other Symptoms	Feeling emotional numbness, guilt, worry, depression, memory loss

There are a variety of options for PTSD treatment ranging from pharmacological interventions to psychotherapy. The first-line pharmacologic treatment is the use of selective serotonin reuptake inhibitors (SSRIs) to reduce clinical symptoms, including suicidal and aggressive behaviors. Some commonly used FDA-approved SSRIs are paroxetine and sertraline. Psychotherapy can be used in an effort to desensitize PTSD patients to triggers, which can be anything that reminds patients of the traumatic event, including places, sounds and smells.[1,4,5] For example, a trigger for a war veteran may be the sound of a helicopter or an unexpected loud noise.[6]

Rationale and evidence

A current area of research for the treatment of PTSD is the use of propranolol, a nonselective beta-adrenergic antagonist that crosses the blood brain barrier. Its current indications include hypertension, angina, supraventricular arrhythmias, tachycardia, migraine headache prophylaxis and myocardial infarction prevention.[4] Propranolol generally has mild and temporary side effects, including sinus bradycardia, hypotension, lethargy, dizziness, nausea and vomiting. Patients with PTSD typically have higher levels of norepinephrine and epinephrine, which induce stress. Epinephrine is thought to aid in memory consolidation, playing a role in the re-experiencing symptoms of PTSD.[7] Beta-blockers inhibit the binding of these neurotransmitters at the receptors (beta-1 and beta-2 for epinephrine, beta-1 for norepinephrine), the proposed clinical mechanism of propranolol.[8] The beta-adrenergic system is associated with response and memory formation as well as the emotional response associated with the memory. Propranolol may both dampen memory formation and dissociate the memory from the emotional response. Although this treatment has been termed "forgetting therapy," it is not meant to make individuals forget their physical experiences but rather enable them to dissociate the emotions and fears from the memories.[9]

In a randomized, double-blind study, 19 subjects were treated with either propranolol or placebo to determine its effects on PTSD.[10] The patients had been diagnosed with PTSD according to the DSM-IV criteria. Traumatic events experienced by individuals in this study included childhood sexual abuse, car accidents, rape, hostage situations, witnessing or experiencing physical assaults, death threats, and house fires. The study began with the preparation of two 20-minute written scripts that investigators turned into 30-second recordings for each patient, including elements of the traumatic experiences that caused their PTSD. Patients then received either 40 mg of short-acting propranolol (nine patients) or an identical placebo (10 patients). If the first dose was well-tolerated, the study group received 60 mg of long-acting propranolol two hours later, while the control group received the placebo. One week later, patients underwent a script-driven imagery procedure where the patients listened to the 30-second recorded scripts and were then asked to imagine the event for 30 seconds. Heart rate (HR), skin conductance (SC) and left corrugator electromyogram (EMG) were recorded. The responses were calculated by subtracting baseline measurements from the average measurements taken during the imagery procedure. Additionally, data from a similar previous study of 152 patients with and without PTSD were included to determine optimal cutoffs for HR, SC and EMG in PTSD patients. The results of the study show that physiological responses to mental imagery of the events were significantly smaller in the propranolol group compared to the placebo. The univariate analysis showed that HR and SC, but not EMG, responses were significantly smaller in the propranolol group. The HR and SC responses for the propranolol group were below the normal cutoffs for PTSD. The placebo group's responses were still above the normal cutoff. The EMG for both groups fell below the normal cutoff. The study suggests that propranolol is effective in controlling physiologic responses to traumatic events in patients if administered after recurrent memories. This evidence lends support towards the rationale of treating certain PTSD patients with propranolol.

A case report, published in 2002, describes the effects of propranolol on a case of re-emergent PTSD after retraumatization. A 44-year-old

Caucasian female experienced five motor vehicle accidents within a 10-year timeframe. Of the five motor vehicle accidents, the last three caused the patient to develop PTSD lasting over six months. It was not until after the third motor vehicle accident that she immediately began experiencing severe PTSD symptoms, including recurrent memories of the event, nightmares, insomnia, flashbacks, irritability and avoidant behavior. Over the span of the seven years that the patient suffered from PTSD, treatment methods included counseling, cognitive and behavioral therapy, and drug regimen trials, including sertraline, imipramine, temazepam and paroxetine with the addition of clonazepam as needed. The patient's PTSD symptoms persisted over the next three years, which gradually dissipated and resolved. Forty-eight hours after her sixth motor vehicle accident, the patient was prescribed propranolol 60 mg to be taken orally twice a day. The Clinician-Administered PTSD Scale (CAPS-Sx) was used to measure changes in PTSD symptoms before, during and after the propranolol treatment. Her first CAPS-Sx score was 86 prior to administration of the propranolol; at the day-11 follow-up visit, the score had dropped to 56. The patient reported feeling much improved as quickly as 48 hours after receiving the propranolol and continued to report improvement until her prescription ran out two months later. The patient's PTSD symptoms resurfaced; therefore, her treatment was resumed. At nine months post-trauma, her CAPS-Sx score was down to 25, her propranolol was discontinued, and she experienced no withdrawal side effects or re-emergence of symptoms.[11]

Future evidence

A 14-week, randomized, double-blind study is currently being conducted to compare propranolol to placebo treatment in PTSD patients. Patients will attend an initial visit, where a medical and psychiatric history review will be obtained, along with a psychiatric interview and symptom questionnaires. Patients with either a DSM-IV diagnosis of PTSD or those meeting five of the six diagnostic criteria for PTSD will be randomly assigned to take a test dose of propranolol or placebo. Following this, patients will be instructed to take the medication subsequent to a traumatic memory associated with hyperarousal symptoms. The patient will utilize a maximum of two doses per day that must be separated by at least six hours. Patients will also use a cognitive therapy-based workbook to track symptoms daily as well as any attempts to use cognitive techniques to relieve symptoms. In addition, patients will attend visits with investigators every two weeks to review workbooks with study officials, pick up medication, discuss side effects, and complete interviews and questionnaires about symptoms. At the conclusion of the trial, a CAPS-Sx Severity Scale will be administered to assess PTSD symptom control, and this will be used as the primary outcome measure. Secondary outcomes will be measured by the Beck Depression Inventory, a Post-Traumatic Scale-Self Score and a Brief Symptoms Inventory-Short Form.[12]

Another randomized, double-blind study being pursued is the use of propranolol in reducing PTSD symptoms through memory reconsolidation in veterans of the wars in Afghanistan and Iraq. As previously stated, it is thought that epinephrine plays a role in strengthening memory consolidation, which leads to persistent memory of the traumatic event(s) for PTSD patients. The idea behind this study using propranolol is to weaken memory reconsolidation by using the drug to block epinephrine binding. Patients in this study will be randomized into either a non-reactivation propranolol group or a post-reactivation propranolol group. At the first visit, non-reactivation propranolol patients will be given propranolol, and post-reactivation propranolol patients will be given a placebo. Two days later, both groups will recall their traumatic event for script preparation, which will trigger the memory reactivation. The non-reactivation propranolol group will receive a placebo, while the post-reactivation propranolol group will receive propranolol. The primary outcome measure at week one and six months will be psychophysiologic responses to script-driven imagery. The anticipation is that the post-reactivation propranolol group will exhibit fewer and less severe responses.[7]

Based on small clinical studies conducted, propranolol may be a viable treatment option for certain PTSD patients. Compared to placebo, small clinical studies have shown propranolol may have significant impact on PTSD symptoms, especially re-experiencing and hyperarousal symptoms. Studies comparing it to other treatment options (SSRIs, tricyclic antidepressants and MAO inhibitors) are limited, and more research needs to be conducted. Propranolol is not currently a first-line therapy, but for those patients that are unresponsive to other treatment options, it should be considered as a means to manage PTSD symptoms.

This is an area of increasing importance to study due to the prevalence of war veterans returning home. PTSD is thought to occur in 11-20 percent of veterans of the wars in Afghanistan and Iraq. PTSD has an impact on quality of life for veterans and their families. Veterans who suffer from this disease may be more prone to develop substance abuse problems, personality disturbances and criminal behavior compared to the general population. Another problem that the veterans face is suicidal tendencies.[13] As troops continue to be deployed, it is important to explore new treatment options since the numbers of PTSD patients is likely to increase. Besides treatment, studies are being conducted to research propranolol in the prevention of PTSD, which may be beneficial to military personnel as well as the civilian population. However, the prophylactic use of propranolol in the military is controversial.[9]

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