Propranolol’s effects on memory reconsolidation in patients with PTSD

Samuel Taibi

Recommended Citation
Taibi, Samuel, "Propranolol’s effects on memory reconsolidation in patients with PTSD" (2019). School of Physician Assistant Studies. 677.
https://commons.pacificu.edu/pa/677

This Capstone Project is brought to you for free and open access by the College of Health Professions at CommonKnowledge. It has been accepted for inclusion in School of Physician Assistant Studies by an authorized administrator of CommonKnowledge. For more information, please contact CommonKnowledge@pacificu.edu.
Propranolol’s effects on memory reconsolidation in patients with PTSD

Abstract

Background: Posttraumatic stress disorder (PTSD) is a psychiatric disorder affecting millions of the US population. Symptoms and comorbidities of the disorder can dramatically affect the lives the sufferers. First-line treatment has been either antidepressants, psychotherapy, or a combination of both. However, success rates are lacking. Recently, the beta blocker propranolol has been shown to have effects on disrupting memory reconsolidation in humans through inhibitory actions on protein synthesis and norepinephrine. This could potentially translate to disrupting the traumatic memories in PTSD and becoming an adequate treatment for the condition.

Methods: An exhaustive literature search of MEDLINE-Ovid, MEDLINE-Pubmed, Google Scholar, and Web of Science with the terms PTSD, Posttraumatic stress disorder, reconsolidation, and propranolol was conducted. Bibliographies were also searched for relevant studies. The studies were evaluated using GRADE criteria.

Results: A search of currently available research yielded 232 articles, 3 of which met inclusion criteria. One of the studies was a meta-analysis from 2013, one study was a continuation from a previous study included in the meta-analysis, and one study was a randomized control trial. Decreases in psychophysiological response (heart rate and skin conductance) to traumatic imagery with propranolol-treated subjects was observed and considered statistically significant. A follow-up study also showed these results lasted over 4 months. Clinician-administered PTSD scale (CAPS) scores and PTSD Checklist (PCL) scores were found to be significantly lower in propranolol-treated PTSD subjects when compared to placebo after memory reconsolidation and at follow-up.

Conclusion: Both early and recent studies have shown promising results of propranolol blocking memory reconsolidation in PTSD patients to reduce symptoms, but its routine use in practice would be premature. Study limitations and uncertainties warrant the need for extension and replication in larger samples of the population. If further studies can duplicate the findings, propranolol use in conjunction with memory reactivation exercises may be an effective, safe, and affordable treatment for PTSD.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

Keywords
PTSD, Posttraumatic Stress Disorder, reconsolidation, propranolol

This capstone project is available at CommonKnowledge: https://commons.pacificu.edu/pa/677
Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu
Propranolol’s Effects on Memory Reconsolidation in Patients with PTSD

Sam Taibi

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, 2019
Faculty Advisor: Allison McLellan, MMS, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Sam Taibi is a native of Colorado where he majored in Health & Exercise Science at Colorado State University in 2012. After completion of his undergraduate degree and being certified through ACSM, he received a job as an exercise physiologist in cardiac and pulmonary rehab. He has worked all over the state of Colorado in his profession, both at hospitals and outpatient clinics. He is happily married to his wife Marissa and have a 2-year-old son named Alexander (A.J.). He also has two dogs named Ricky and Lucy. He and his family enjoy traveling around both Colorado and Oregon and exploring whatever the world has to offer.
Abstract

Background: Posttraumatic stress disorder (PTSD) is a psychiatric disorder affecting millions of the US population. Symptoms and comorbidities of the disorder can dramatically affect the lives of sufferers. First-line treatment has been either antidepressants, psychotherapy, or a combination of both. However, success rates are lacking. Recently, the beta blocker propranolol has been shown to have effects on disrupting memory reconsolidation in humans through inhibitory actions on protein synthesis and norepinephrine. This could potentially translate to disrupting the traumatic memories in PTSD and becoming an adequate treatment for the condition.

Methods: An exhaustive literature search of MEDLINE-Ovid, MEDLINE-Pubmed, Google Scholar, and Web of Science with the terms PTSD, Posttraumatic stress disorder, reconsolidation, and propranolol was conducted. Bibliographies were also searched for relevant studies. The studies were evaluated using GRADE criteria.

Results: A search of currently available research yielded 232 articles, 3 of which met inclusion criteria. One of the studies was a meta-analysis from 2013, one study was a continuation from a previous study included in the meta-analysis, and one study was a randomized control trial. Decreases in psychophysiological response (heart rate and skin conductance) to traumatic imagery with propranolol-treated subjects was observed and considered statistically significant. A follow-up study also showed these results lasted over 4 months. Clinician-administered PTSD scale (CAPS) scores and PTSD Checklist (PCL) scores were found to be significantly lower in propranolol-treated PTSD subjects when compared to placebo after memory reconsolidation and at follow-up.

Conclusion: Both early and recent studies have shown promising results of propranolol blocking memory reconsolidation in PTSD patients to reduce symptoms, but its routine use in practice would be premature. Study limitations and uncertainties warrant the need for extension and replication in larger samples of the population. If further studies can duplicate the findings, propranolol use in conjunction with memory reactivation exercises may be an effective, safe, and affordable treatment for PTSD.

Keywords: PTSD, Posttraumatic Stress Disorder, reconsolidation, propranolol
Acknowledgements

To Marissa and AJ: Thank you for your love and understanding. You two are my rock and my inspiration. I love you both very much.

To my parents: Thank you for helping me to succeed and for supporting me for all these years. I love you both.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biography</td>
<td>2</td>
</tr>
<tr>
<td>Abstract</td>
<td>3</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>5</td>
</tr>
<tr>
<td>List of Tables</td>
<td>6</td>
</tr>
<tr>
<td>List of Abbreviations</td>
<td>6</td>
</tr>
<tr>
<td>Background</td>
<td>7</td>
</tr>
<tr>
<td>Methods</td>
<td>10</td>
</tr>
<tr>
<td>Results</td>
<td>10</td>
</tr>
<tr>
<td>Discussion</td>
<td>24</td>
</tr>
<tr>
<td>Conclusion</td>
<td>27</td>
</tr>
<tr>
<td>References</td>
<td>29</td>
</tr>
<tr>
<td>Table 1: Quality Assessment of Reviewed Articles</td>
<td>33</td>
</tr>
</tbody>
</table>
List of Tables

Table 1: Quality Assessment of Reviewed Studies

List of Abbreviations

PTSD  Posttraumatic Stress Disorder
SSRI  Selective Serotonin Reuptake Inhibitor
SNRI  Selective Norepinephrine Reuptake Inhibitor
NE   Norepinephrine
RCT  Randomized Control Trial
SA   Short-acting
LA   Long-acting
HR   Heart rate
SC   Skin conductance
EMG  Left corrugator electromyogram
CAPS Clinician-Administered PTSD scale
PCL  PTSD Checklist
ITT  Intention-to-Treat Analysis
PP   Per protocol Analysis
Propranolol’s Effects on Memory Reconsolidation in Patients with PTSD

BACKGROUND

Posttraumatic stress disorder (PTSD) is a psychiatric disorder arising from a traumatic event that has a lifetime prevalence rate of 4-6% in the United States. These events typically include rape, childhood abuse, domestic disputes, unexpected deaths/conditions of loved ones, experiencing physical injuries from medical issues, physical assault, exposure to organized violence, combat exposure, motor vehicle accidents, and natural disasters. People suffering from PTSD commonly experience disturbing and intense thoughts related to their trauma which can include nightmares, flashbacks, anxiety, fear, combativeness, anger, sadness, depression, avoidance, derealization, physiological overactivity, and depersonalization. These clinical manifestations often dramatically affect the individual in many areas of their life long after the original trauma. Comorbid conditions include other psychiatric disorders, cardiovascular and gastrointestinal disease, diabetes, arthritis, hypertension, and autoimmune disorders.

First-line therapy for PTSD has been psychotherapy alone or with medications, such as selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs). However, the
evidence of success rates are lacking.\textsuperscript{7,8} SSRIs and SNRIs are the most commonly used medications for PTSD but can have significant side effects such as sexual dysfunction, insomnia, and increased anxiety. Psychotherapy alone has not been found to adequately treat PTSD.\textsuperscript{8} Combined therapy with SSRIs and psychotherapy has also not been found to effectively treat PTSD symptoms.\textsuperscript{9} Clearly, new approaches to treatment need to be considered.

Recently, a new approach to treating PTSD involves disrupting the reconsolidation of traumatic memories. The initial consolidation of memories involves transferring new memories from short to long-term memory. This is a complex process involving protein synthesis, synaptic consolidation within the first few hours of acquiring a new memory, and systems consolidation, where hippocampus-dependent memories become independent of the hippocampus over a period of weeks to years as the memory is continuously recalled.\textsuperscript{10} The consolidation process is thought to make the memory stable in long-term memory storage. Conversely, memory reconsolidation involves accessing these consolidated memories and reconsolidating them, once again, into long-term memory storage. However, during the memory reconsolidation process, the retrieved memory is thought to be labile or malleable due to the reconsolidated memory going through some of the same processes that occur during consolidation, most
notably protein synthesis.\textsuperscript{11–14} Altering or disrupting this reconsolidation process is thought to be a target in modifying or updating PTSD memories and symptoms.

One of the medications being studied to alter the reconsolidation process is the beta blocker propranolol. Propranolol is a nonselective, beta-adrenergic blocker of epinephrine, norepinephrine (NE), and voltage-gated sodium channels.\textsuperscript{15} Its mechanism of action blocking peripheral beta receptors and voltage-gated sodium channels is useful for such conditions like hypertension, tremor, tachyarrhythmias, and coronary artery disease. Propranolol is also lipophilic and can cross the blood brain barrier exerting inhibitory effects on the central nervous system, aiding in the treatment of migraine.\textsuperscript{16} This central inhibitory effect is also one target of memory reconsolidation therapy for treatment of PTSD symptoms through effects on protein synthesis in the amygdala, which has been found to be hyper responsive in PTSD patients.\textsuperscript{17–19} The other proposed therapeutic use of propranolol is the effect of blocking NE as NE is important in the encoding, retrieval and reconsolidation of emotional memory.\textsuperscript{20} Patients with PTSD have been found to have elevated levels of NE in their cerebrospinal fluid when compared to healthy individuals.\textsuperscript{21}
Studies have shown conflicting findings for propranolol to prevent the development of PTSD immediately after trauma exposure; however, relatively few studies have been performed examining propranolol’s inhibitory effects on long-term memory reconsolidation. Can propranolol effectively diminish memory reconsolidation in PTSD patients?

METHODS

An exhaustive literature search of MEDLINE-Ovid, MEDLINE-Pubmed, Google Scholar, and Web of Science was conducted using the keywords: PTSD, posttraumatic stress disorder, reconsolidation, and propranolol. Bibliographies were also searched for relevant studies. Further refinement of search strategies included studies relevant to the topic, data extracted from human studies, and studies done in the English language. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

RESULTS

The initial search yielded 232 results, some of which were duplicates. One of the returned results was a meta-analysis from 2013 evaluating propranolol’s effects on long-term emotional memory. Memory reconsolidation blockade in PTSD was included as a subsection.
of the meta-analysis and only the results from the 2 studies\textsuperscript{24,25} evaluating those specific parameters were included in this systematic review. Following elimination of duplicate studies and screening of relevant articles performed in human populations and in the English language, a total of another 2 relevant studies, done since 2013, met eligibility criteria and were included. One of the included articles\textsuperscript{26} was a continuation of a previous study included in the meta-analysis which was an open-label study. The other relevant study was a randomized control trial (RCT).\textsuperscript{27} See Table 1.

**Lonergan et al**

Lonergan et al\textsuperscript{22} conducted a meta-analysis in 2013 to assess propranolol’s effects on consolidation and reconsolidation of long-term emotional memory. For the sake of this review, only the studies regarding memory reconsolidation in PTSD patients will be discussed. Both of these studies were performed by Brunet et al.\textsuperscript{24,25}

**Study 1** - The purpose of this study by Brunet et al\textsuperscript{25} was to examine the effects of trauma post-reactivation propranolol use on physiologic responses as compared to placebo.

Nineteen participants with chronic PTSD, according to DSM-IV, described the traumatic event that caused their PTSD as a means of reactivating their traumatic memory in writing. Immediately following
reactivation, participants were either given 40 mg of short-acting (SA) propranolol followed 2 hours by 60 mg long-acting (LA) propranolol or similar appearing placebo capsules. Later, a researcher composed and recorded 30 second scripts portraying the traumatic event. One week later, subjects returned and listened to the recorded scripts while imagining the event. Measured physiologic responses were measured at baseline and during the reactivation script and included heart rate (HR), skin conductance (SC) and left corrugator electromyogram (EMG). The optimal PTSD cut-offs for these measurements were previously determined using data from 152 individuals with (n = 79) or without (n = 72) PTSD who had gone through the same procedure. Responses were calculated by subtracting the mean baseline physiological measurements from the mean imagery period measurements. The participants were randomized by the study’s physician with 9 of the participants receiving propranolol and 10 participants receiving placebo. The physician kept the other investigators and the subjects blind as to his allocation. He did not participate in the experimental protocol outside of administering medication and medical monitoring.

Results showed physiologic responding to the traumatic event was significantly smaller in the participants who received propranolol (p=0.007). HR and SC were determined to be the most significantly
lowered values in the propranolol group compared to the placebo group by univariate analyses.

**Study 2** - This study, conducted by Brunet et al (2011), consisted of 3 open-label trials which explored if more significant improvements could be seen in participants administered propranolol with trauma reactivation exercises over a greater number of treatment sessions and if the improvement was longer lasting.

Inclusion criteria included participants aged 18 to 65 years of age meeting DSM-IV criteria for chronic PTSD. Exclusion criteria included: history of traumatic brain injury; a current or past psychotic, bipolar, or substance dependence disorder; a previous adverse reaction to a beta blocker; current use of medications that could adversely interact with propranolol; conditions such as asthma, heart problems, or diabetes that would contraindicate the use of propranolol; pregnancy or breast feeding; or participation if any form of psychotherapy.

**Trial 1.** This study involved 28 participants recruited via the newspaper in Montreal, Canada who would be evaluated at pretreatment, 6 weekly treatment sessions. The participants all had experienced a traumatic event meeting criterion A for PTSD diagnosis and included motor vehicle accidents, participation in a military UN
peacekeeping mission, physical assault, assault with a weapon, sexual abuse, incest, physical abuse in childhood, or others. Comorbid conditions in participants included major depressive disorder (n=8), social phobia (n=8), obsessive-compulsive disorder (n=6), generalized anxiety (n=5), panic disorder with or without agoraphobia (n=7), anorexia nervosa (n=1), and bulimia (n=3). Participants were reimbursed up to $250 on a pro-rated basis.24

PTSD symptom measurement and diagnosis was determined by the Clinician-Administered PTSD scale (CAPS) before and after treatment and at follow-up. Timing of the follow-up was unspecified. Additionally, the PTSD checklist (PCL) was given weekly during the 6 treatments to determine intersession improvement. PTSD was diagnosed with the Structured Clinical Interview for DSM-IV.24

A dose of 0.67 mg/kg of SA oral propranolol was administered during the first session. Ninety minutes later, an additional 1 mg/kg of LA oral propranolol was given. LA propranolol was not given if systolic blood pressure (BP) decreased by 10 mm Hg or more to lower than 100 mm Hg and if the SA dose was not tolerated well. The average doses given were 47.8 mg SA and 71.1 mg LA. Immediately after given the LA dose, participants provided a written account of the traumatic event that led to their PTSD. During subsequent sessions,
SA and LA propranolol doses were given simultaneously. Ninety minutes later, subjects were instructed to read aloud the written account of their traumatic event.\textsuperscript{24}

Results showed mean CAP score improvements at pretreatment, posttreatment, and follow-up (71.8, 45.8, and 42.7; \( p<0.001 \), respectively). Twenty of the 28 participants no longer met full criteria for PTSD at follow-up. PCL scores also significantly decreased across time (\( p<0.001 \)).\textsuperscript{24}

\textit{Trial 2.} This trial involved 7 participants recruited by word of mouth in Boston, Massachusetts. Provoking traumatic events included motor vehicle accident, physical assault, assault with a weapon, rape, witness to family member’s illness, and military combat. Comorbidity included major depressive disorder (\( n=3 \)) and panic disorder without agoraphobia (\( n=2 \)). Assessment using CAPS was identical to trial 1 with a specified follow-up at six months. PCL scores were not used. Propranolol administration protocol was the same as trial 1; however, this study used fixed doses of 40 mg SA and 80 mg LA. Participants also provided an oral account of the initiating traumatic event rather than a written account during the first session. In subsequent sessions, the account was orally repeated to initiate reactivation.\textsuperscript{24}
Five of the 7 participants no longer met PTSD diagnostic criteria at follow-up. Mean CAPS scores significantly decreased (pretreatment 68.4, posttreatment 35.6, and follow-up 34.1).24

Trial 3. The trial, set in Toulouse, France, was part of an ongoing longitudinal study examining the long-term effects of an industrial disaster and involved 32 participants. This trial was unique in that it had a control group of 25 subjects who refused treatment but agreed to be a part of the study. Seven participants were treated with propranolol. Outcome measures were PCL scores measured at 6 months post-disaster, before treatment, after treatment, and follow-up at six months. Treated subjects took part in 6 treatment sessions, similar to trial 1 and 2. Comorbidity in treated participants included major depressive disorder, generalized anxiety disorder, and agoraphobia without panic. Propranolol administration at first visit was the same as trial 2. Subsequent sessions only administered 80 mg of LA propranolol. Treatment protocol of reactivation was identical to trial 1.24

Mean PCL scores in the treatment group at 6 months post-disaster, pretreatment, posttreatment, and follow-up were 60.9, 60.7, 41.0, and 38.4, respectively. Control group values were 59.7, 61.7, 58.7, and 58.7. Groups did significantly differ at posttreatment and
follow-up (p < 0.01). Six of the 7 treated participants no longer met the criteria for PTSD at follow-up, compared with 2 (8%) of the 25 untreated participants (P < 0.001).

**Brunet et al (2014)**

Brunet et al\(^2\) conducted a continuation study in 2014 from a previous open-label trial done in 2011.\(^2\)\(^4\) In a previous study, discussed in the meta-analysis, Brunet et al\(^2\)\(^5\) demonstrated that participants with PTSD showed lower physiologic response during script-driven traumatic imagery 1 week after receiving a single dose of propranolol given after the retrieval of a traumatic memory. This study lacked an adequate follow-up to determine if the effects were long-lasting. The purpose of this 2014 study was to determine if these physiological effects were also seen in participants from the previous open-label trial done in 2011, which was a longer duration study.\(^2\)\(^4\) The 2011 study results are discussed above.

An independent research assistant conducted a script-driven imagery procedure between treatment and posttreatment in 22 participants from the 2011 study. Two of the original participants were lost to follow-up and 4 had unusable SC data. This was done 1 week after the treatment of 6 weekly visits where participants read an account of their traumatic event following oral administration of 0.67
mg/kg of SA propranolol and 1 mg/kg of LA propranolol. The patients SC, HR, and left corrugator EMG were recorded during a 30-second baseline period and a period after listening to 4 audio-recorded scripts (2 portraying the participant’s traumatic event and 2 portraying neutral events), where participants “imagined the event as if it were happening” for 30 seconds. The change in physiological scores was calculated by subtracting the baseline mean value from the mean value of the imagery period that followed the scripts. There was also a 26-week follow-up where the same procedure was replicated.27

A composite measure of psychophysiological reactivity during imagery was obtained on each participant. This provided a single score (posterior probability) displaying a person’s overall psychophysiological reactivity during imagery and the likelihood that their score belonged to a calibration sample’s PTSD group. The calibration sample consisted of HR, SC, and EMG responses from previously studied participants27 who had been exposed to trauma and either had or did not have PTSD. The previous participants with a posterior probability greater than 0.5 were considered to have a greater than 50% chance of having a current diagnosis of PTSD and were put into the PTSD group. If the participants had a posterior probability less than 0.5, they were assigned to the non-PTSD group.27
The posttreatment HR, SC, and EMG responses from the 22 participants were then compared with responses from the initial psychophysiological study\textsuperscript{25} where 9 patients received placebo and 10 patients received propranolol.\textsuperscript{27}

According to the discriminant function analysis, 20 (91\%) of the 22 participants were classified as non-PTSD at posttreatment. Twenty-one (96\%) of the participants were classified as non-PTSD at follow-up.\textsuperscript{27}

MANOVA and ANOVA analyses comparing the 22 current propranolol participants, the 10 previous propranolol patients, and the previous 9 placebo patients found a significant main effect for physiological responding (p < 0.05) and significant group differences for SC (p < 0.001) and HR (p < 0.05), but not EMG (p = 0.48). The mean score of the current propranolol group’s SC and HR was significantly smaller than the previous placebo group. There were no significant differences between the present and previous propranolol groups for SC or HR.\textsuperscript{27}
Brunet et al (2018)

This recent RCT\textsuperscript{28} from 2018 was aimed at evaluating the efficacy of using propranolol during trauma memory reactivation exercises to reduce symptoms of PTSD.

Participants were recruited via referrals and local advertisement. Inclusion criteria included: patients aged 18-65 years of age with PTSD who were seeking treatment, patients who had PTSD for at least 6 consecutive months, patients who scored $\geq 44$ on the PCL-S at intake, patients who were fluent in French or English, and patients who lived in Montreal. Exclusion criteria included: basal HR $<55$ beats per minute, medical conditions (asthma, diabetes, arrhythmia, or congestive heart failure) that would contraindicate the use of propranolol, lifetime psychotic or bipolar disorder, traumatic brain injury, current substance dependence, acute suicidal ideation, current use of medication that could interact adversely with propranolol (anti-arrhythmic or calcium channel blocker), pregnant or breast feeding, receipt of psychotherapy for PTSD during treatment phase, involvement in PTSD-related litigation, or strong dissociative tendencies (average score of $>20$ on the Dissociative Experiences Scale). Patients taking antidepressants were included in the study but were asked to delay their medication by a few hours on treatment
days. A total of 61 participants met inclusion criteria and were randomly assigned to six treatment sessions. One participant from the placebo group was excluded due to invalid data, leaving 30 participants to be analyzed in the active treatment group and 30 participants in the placebo group. Participants who adhered to the study at the seventh- and twenty-sixth-week assessments were given $50. Follow-up was conducted at 6 months.28

The CAPS and PCL-S were used to assess effectiveness of treatment. The Mini International Neuropsychiatric Interview version 5.0 was used to assess pretreatment comorbidity of 17 other DSM IV axis I mental disorders. CAPS was administered 1 week before, 1 week after, and 6 months follow-up treatment to provide a PTSD symptom score and a formal DSM IV diagnosis of PTSD. The PCL-S was administered at the beginning of each treatment session, before propranolol administration, to assess the previous week’s symptoms. The CAPS and PCL-S scores were compared between baseline and posttreatment. CAPS follow-up data were only available for 14 participants.28

As in previous studies,24 0.67 mg/kg of SA oral propranolol, plus 1.0 mg/kg of LA propranolol was given. However, during the first session, instead of 90 minutes elapsing between doses, they used a 2-
hour delay to assess for adequate medication tolerance. Also, during subsequent sessions they administered both medications concurrently.28

They used the Douglas Institute pharmacy at McGill University to maintain randomization schedule and to prepare and dispense the medication. All medication packages were the same and empty packets were kept in the participant’s file to assess for adherence.28

Vital signs and symptoms were monitored before administration and every 30 minutes for 90 minutes until trauma reactivation exercises began. Six of the 60 participants reported side effects and were excluded from further participation.28

Trauma reactivation was performed by a doctorate-level therapist who was blinded to group status and trained by the lead author, Alain Brunet. At 1 hour after medication administration, the participants were instructed to write a single page narrative about the trauma they experienced focusing on the event’s most disturbing moments and including 5 or more bodily sensations drawn from a checklist. The participant was then asked to read the written narrative aloud “as if they were back in the event.” During each subsequent visit, the participants were asked if they needed to add or remove any details to the narrative before once again reading it aloud.28
The researchers performed an intention-to-treat analysis (ITT) on the initial 60 participants and a per protocol analysis (PP) on the 30 participants (15 treatment, 15 placebo) who completed at least 5 treatment sessions. Analysis of covariance was used to test for a between-group difference in post-treatment CAPS score and adjusted for pretreatment score.\(^{28}\)

Results displayed decreased CAPS scores in both groups for ITT analysis (propranolol mean baseline and posttreatment, 76.07 and 47.16; placebo mean baseline and posttreatment, 71.04 and 53.69), but decreases were significantly higher in the propranolol group. The estimated posttreatment between-group difference, which was adjusted for baseline score, was 11.50 (p=0.034). The ITT and PP pre- to posttreatment CAPS improvements were 38% and 36% in the propranolol group and 24% and 13% in the placebo group, respectively. Results were similar for PP scores with an estimated posttreatment between-group difference of 16.30 (p=0.037).\(^{28}\)

PCL-S scores also decreased in both groups for ITT with higher decreases in the propranolol group (propranolol mean baseline and posttreatment, 61.18 and 36.60; placebo mean baseline and posttreatment, 61.27 and 55.71). The intention-to-treat and per protocol pre- to posttreatment PCL-S improvements, respectively,
were 56% and 53% in the propranolol group and 15% and 10% in the placebo group. PCL-S scores decreased an average of 2.43 points per week in the ITT analysis and 2.79 points in the PP analysis in the propranolol group.28

DISCUSSION

All the studies24-28 included in this review found that propranolol had beneficial effects on PTSD symptoms in patients who took the medication either before or after the memory reconsolidation technique. The administration of propranolol along with memory reactivation decreased mean CAPS scores up to 38% in the RCT conducted by Brunet et al (2018)28 with up to 70% of subjects no longer meeting PTSD diagnostic criteria in the open-label trials.24 PCL scores decreased anywhere from 45% to 56% from pretreatment to posttreatment.24,28 Psychophysiological responses such as HR and SC to trauma reactivation decreased to levels of trauma patients without PTSD when compared to placebo,25 and the results were enduring.27 Other case studies have shown similar effects in treating PTSD symptoms during memory reconsolidation with propranolol after only one to two treatment sessions.29

The study from 2007,25 specifically examining the effects on physiological responses, administered the propranolol immediately
following the first reactivation exercise. In contrast, all of the remaining studies administered the medication prior to the trauma memory reactivation. Potentially, administering propranolol before reactivation could lead to effects on retrieval of the material. In the meta-analysis, this issue is discussed. Studies have found that propranolol has no effect on brain mechanisms activated during reactivation, ruling out any effects on retrieval of the memory, although this could be potentially studied more in detail.

Although Brunet et al used propranolol following memory retrieval in the 2007 study, he explains that due to reconsolidation starting 3-10 minutes after memory reactivation, most reconsolidation done in the first 2 hours, and with propranolol reaching peak bioavailability in 90 minutes, the administration of propranolol following memory retrieval may be too late to be effective. This was also examined in a later study. As a result of this, Brunet and his colleagues opted to use propranolol before reactivation in later studies, despite showing decreased physiological responses with post-reactivation propranolol administration in his 2008 study. Interestingly, in a comparative study where researchers provided propranolol prior to reactivation in combat-related PTSD subjects, results failed to replicate the findings of Brunet et al’s.
In all the studies,\textsuperscript{24-28} reconsolidation of memories through reactivation was the target for propranolol’s usage. However, it is difficult to determine if propranolol was actually blocking reconsolidation or enhancing extinction.\textsuperscript{33} In Brunet et al’s studies,\textsuperscript{24,27,28} participants either described or listened to their traumatic event continually over multiple treatments. This, in effect, could be considered extinction training since they were continually exposed to their traumatic event. Brunet et al (2007)\textsuperscript{24} did attempt to minimize the effects of extinction by maintaining a shorter treatment session, but it is difficult to distinguish whether the effect was due to reconsolidation, extinction, or a combination of both. Brunet goes on to further explain that reconsolidation differs from extinction in that extinction training typically has longer treatment periods and that extinction training tends to inhibit traumatic memories, while reconsolidation blockade has a tendency to weaken or erase the original memory in a shorter amount of time.\textsuperscript{24,28}

Other methods of interfering with reconsolidation have been considered. The Reconsolidation of Traumatic Memories Protocol (RTM) has recently shown promising results.\textsuperscript{34-35} The process of memory reactivation and reconsolidation are essentially the same, however, participants are taken through a series of visual imagery exercises to dissociatively modify or restructure the traumatic
memory. The protocol is completed over the course of three to five 90-minute long sessions administered over a five to ten-day period. In one study, 26 male veterans completed the RTM protocol with a mean-treatment reduction of 33 points on the PCL military version (PCL-M) after 6 weeks. Studies could potentially be conducted using both propranolol and RTM, or comparing the two, to further expand the research being conducted on memory reconsolidation blockade.

Obviously, there were limitations to the studies included, along with possible bias. Larger sample sizes would be of benefit along with adequate follow-up. Follow-up values were obtained in some studies although some had lost an adequate number of participants, which could lend to a risk for attrition bias. The extent of blinding and allocation was discussed in some studies, but did not adequately address the degree to which blinding occurred for participants and researchers, alike. Additionally, Alain Brunet, Ph.D. was included in each study which could potentially lead to publication bias.

CONCLUSION

Studies have shown promising results of propranolol blocking memory reconsolidation in PTSD patients to reduce symptoms, but its
routine use in practice would be premature. Study limitations and uncertainties warrant the need for extension and replication in larger samples of the population. If further studies can duplicate the findings, propranolol use in conjunction with memory reactivation exercises may be an effective, safe, and affordable treatment for PTSD.
References


9. Hetrick SE, Purcell R, Garner B, Parslow R. Combined pharmacotherapy and psychological therapies for post traumatic...


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Study Designs</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of Physiological Responses&lt;sup&gt;24,27&lt;/sup&gt;</td>
<td>2</td>
<td>Open-label, Case control studies</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not Serious&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reduction of CAPS and CPL-S Scores&lt;sup&gt;24,28&lt;/sup&gt;</td>
<td>2</td>
<td>Open-label, RCT</td>
<td>Not Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;d,f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Lack of blinding of data collectors and patients in both

<sup>b</sup>Unclear whether propranolol works directly on memory reconsolidation, although it is hypothesized

<sup>c</sup>Did not include results of physiological testing in original open-label study. Results of this were disclosed in future study.

<sup>d</sup>Small sample size

<sup>e</sup>Alain Brunet is an author included in every study

<sup>f</sup>Risk of attrition bias