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Is Propranolol Administration Following a Traumatic Event Effective in Reducing Symptoms of Post-Traumatic Stress Disorder?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not propranolol administration following a traumatic event is effective in reducing symptoms of post-traumatic stress disorder (PTSD).

Study Design: Review of three English language randomized, double-blind, placebo-controlled clinical trials published in 2002, 2007, and 2010.

Data Sources: Three randomized, double-blind, placebo-controlled clinical trials found using PubMed and Cochrane Library databases.

Outcome(s) Measured: The incidence of PTSD symptoms was measured in patients following traumatic events after the administration of propranolol. This was done using The Screening Tool for Early Predictors of PTSD, the Clinician Administered PTSD Scale for Children and Adolescents, the Clinician Administered PTSD Scale (CAPS), Script-driven Imagery, The Acute Stress Disorder Scale, the CIDI Modules for PTSD, MDD, and panic disorder, the DSM-IV, and The Posttraumatic Stress Disorder Checklist.

Results: Three randomized, double-blind, placebo-controlled studies comparing propranolol to placebo were reviewed. The Nugent study demonstrated a clinical benefit of propranolol vs. placebo in PTSD symptoms in a pediatric sample. The Pitman study showed inconclusive results for using propranolol over placebo in incidence of PTSD symptoms in an adult sample. The Stein study did not show a difference in incidence of PTSD symptoms in propranolol vs. placebo in an adult sample.

Conclusion: While it remains inconclusive at this time as to the benefit of propranolol in reducing PTSD symptoms, two of the trials support the clinical feasibility of this hypothesis. Further studies are warranted to investigate the relationship between propranolol administration and the development of PTSD symptomatology.

Key Words: Propranolol, Post-Traumatic Stress Disorder

INTRODUCTION

Post-traumatic stress disorder (PTSD) is defined as a pathological anxiety that usually occurs after an individual experiences or witnesses severe trauma that constitutes a threat to the physical integrity or life of the individual or another person[1]. PTSD affects 7.7 million Americans annually, and the current lifetime prevalence is estimated to be 6.8%[1, 2].

While it is difficult to calculate the total amount of health care dollars spent on PTSD in the United States every year, it is thought that the annual cost to society of anxiety disorders exceeds 42 billion dollars per year[2]. Cost continues to be a major issue in PTSD treatment, especially for veterans. During fiscal years 2004-2009, the Veterans Health Administration spent 60% of its funding on patients with PTSD, Traumatic Brain Injury (TBI), or both, totaling 2.2 billion dollars[3]. It is thought that the number of patients suffering from PTSD is thought to be much higher than the number of individuals seeking help. And while the exact number of annual health care visits for PTSD remains unknown, it is estimated that between 5 and 7 million Americans seek help for PTSD each year[1,2,3].

There is no one cause for PTSD, but the condition is believed to be caused by a combination of a wide range of traumatic events, genetics, coping styles, lack of social support, and neurobiology. The disorder is characterized by disturbing recurrent flashbacks, avoidance of memories of the event, and hyper-arousal[2]. Studies have found that combat experience, childhood trauma, chronic adversity, familial stressors, drug misuse, and an upbringing in foster care put individuals at an increased risk for PTSD[2]. It appears that PTSD shares many of the same genetic influences with other psychiatric disorders. Studies have shown that panic, generalized anxiety disorders, and PTSD share 60% of the same genetic variance[4].

Usual methods for treating PTSD may include Cognitive Behavioral Therapy (CBT), Exposure Therapy, and Eye Movement Desensitization and Reprocessing[1, 2]. Medications constitute a large role in the treatment of PTSD, and medications used include SSRIs (ex. sertraline, fluoxetine), benzodiazepines (ex. lorazepam, diazepam), and anticonvulsants and mood stabilizers (ex. carbamazepine, topiramate, lamotrigine) [1, 2]. Current treatments of PTSD focus on managing the signs and symptoms of the condition through various therapies and medications, yet little research has been done on strategies to prevent the development of PTSD following a traumatic event. One such drug hypothesized to prevent the development of PTSD symptoms is the non-selective beta-blocker propranolol, a drug whose action works through inhibiting the body's response to sympathetic nerve impulses. Due to propranolol's effect on beta-adrenergic receptors, it is theorized that propranolol administration following a traumatic event may inhibit the formation of traumatic memories by preventing stimulation of norepinephrine on the amygdala[5, 6, 7].

OBJECTIVE

The objective of this systematic review is to determine whether or not propranolol administration following a traumatic event is effective in reducing symptoms of PTSD.

METHODS

Three randomized, double-blind, controlled clinical trials were utilized in this review. Interventions included propranolol administration at various doses following an acutely traumatic event in populations deemed at risk for PTSD; these populations included pediatric injury patients, patients following an acutely traumatic event, and surgical trauma center patients.

Comparisons were made to administration of placebo, and in one study, administration of gabapentin. Outcomes measured were incidence of PTSD symptoms in the selected populations.

Key words used in the search consisted of “propranolol”, “post-traumatic stress disorder”, and “PTSD”. All articles were published in English and in peer reviewed journals. The author undertook the search for articles using Medline and Pubmed, and articles were selected based on their relevance to the clinical question as well as inclusion of patient oriented evidence that matters (POEMs). Inclusion criteria consisted of articles utilizing randomized, controlled, double blind trials. Exclusion criteria consisted of studies published before 1996 or studies using disease-oriented outcomes (DOE). The statistics used and reported in the studies include control event rate (CER), experimental event rate (EER), absolute risk reduction (ARR), and number needed to treat (NNT). Demographics and characteristics of the studies are shown in Table 1.

Table 1: Demographics and Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Nugent[5] (2010)	RCT	29	10-18	age 10-18 at risk for PTSD within 12 hours of admission; GCS score > 14	hypersensitivity to beta-blockers, bradycardia, cardiogenic or hypovolemic shock, diabetes, preexisting heart condition, treatment for asthma, or if injuries or medical treatment contraindicated propranolol	0	oral solution of propranolol (HCL 20 mg/5 ml) b.i.d. for 10 days
Pitman[6] (2002)	RCT	41	n/a	Emergency Department patients who had just experienced a traumatic event	serious physical injury, substance intoxication, pregnancy, or lifetime history of congestive heart failure, heart block, or asthma, HR < 80 bpm, systolic BP < 100 mm Hg	10	40 mg oral propranolol 4x daily for 3 months
Stein[7] (2007)	RCT	48	18-65	Pts admitted to the University of California Level 1 Surgical Trauma Center	Lived too far for home monitoring, medically unstable, not English speaking, age . 65 or < 18, suicidal, homeless, jail or police hold, cardiac or seizure medications, active military	10	Propranolol started at 20 mg t.i.d. and uptitrated over 2 days to 40 mg t.i.d. x 8 days, followed by taper x 4 days.

OUTCOMES MEASURED

The incidence of PTSD symptoms was measured in patients following traumatic events after the administration of propranolol. This was done using The Screening Tool for Early Predictors of PTSD, the Clinician Administered PTSD Scale for Children and Adolescents, the Clinician Administered PTSD Scale (CAPS), Script-driven Imagery, The Acute Stress Disorder Scale, the CIDI Modules for PTSD, MDD, and panic disorder, the DSM-IV, and The Posttraumatic Stress Disorder Checklist.

RESULTS

The three double-blind, randomized clinical trials in this systematic review compared the effect of propranolol administration vs. administration of placebo in reducing incidence of PTSD symptomatology following a traumatic event. All three studies use dichotomous data.

In the Nugent study, 29 pediatric injury patients between the ages of 10-18 at risk for PTSD were randomized to a double blind 10 day trial of propranolol vs. placebo. The propranolol and placebo were administered to the patients within 12 hours of their admission to the emergency department and PTSD symptoms were assessed after 6 weeks. Eligibility criteria included an “at risk” for PTSD using The Screening Tool for Early Predictors of PTSD and a Glasgow Coma Scale score of 14 or greater. The subjects were administered an oral solution of propranolol (HCL 20 mg/5 ml) or liquid placebo twice daily for 10 days. An in-home follow-up assessment was undertaken 6 weeks post-trauma where the children were asked to give a 5 minute narrative of their trauma followed by administration of the Clinician Administered PTSD Scale for Children and Adolescents (CAPS-CA). Results are seen below in Tables 2, 3, and 4.

Table 2: Efficacy of Propranolol vs. Placebo in the Nugent et al. Study

	All subjects (n = 26)	Propranolol (+/- SD)	Placebo (+/- SD)
Mean CAPS-CA Score at 6 weeks post-trauma	24.4 (+/- 19.0)	27.8 (+/- 24.1)	21.6 (+/- 13.8)

Table 3: PTSD Rates in Nugent et al. Study, 6 Week Follow-Up

	Propranolol (n=12)	Placebo (n=14)
Number of patients meeting at least partial PTSD criteria 6 weeks post-trauma	42%	58%

Table 4: Absolute Risk Reduction and Number Needed to Treat Nugent et al. Study, 6 Week Follow-Up

CER	EER	ARR	NNT
58%	42%	16%	1/16% = 7

The Pitman study randomized 41 emergency department patients who had just experienced a traumatic event that met the DSM-IV PTSD A.1 (stressor) and A.2 (response) criteria. Subjects were randomized to receive either 40 mg of propranolol or placebo as soon as possible after the event and no longer than 6 hours after the traumatic event. Upon discharge from the emergency department, the patients were instructed to continue the medication four times daily as tolerated for 10 days. This was then to be followed by a 9 day taper period. One and three months later, the subjects were asked to return to be administered the Clinician-Administered PTSD Scale (CAPS) by a highly trained psychologist. Results are shown below in Tables 5, 6, 7, and 8.

Table 5: Efficacy of Propranolol vs. Placebo in the Pitman et al. Study, 1 Month Follow-Up

	Propranolol (+/- SD)	Placebo (+/- SD)
Mean CAPS Score	27.6 (+/- 15.7)	35.5 (+/- 21.5)
PTSD Rate	18%	30%

Table 6: Absolute Risk Reduction and Number Needed to Treat Pitman et al. Study, 1 Month Follow-Up

CER	EER	ARR	NNT
30%	18%	12%	1/12% = 9

Table 7: Efficacy of Propranolol vs. Placebo in the Pitman et al. Study, 3 Month Follow-Up

	Propranolol (+/- SD)	Placebo (+/- SD)
Mean CAPS Score	21.1 (+/- 12.5)	20.5 (+/- 21.7)
PTSD Rate	11%	13%

Table 8: Absolute Risk Reduction and Number Needed to Treat in Pitman et al. Study, 3 Month Follow-Up

CER	EER	ARR	NNT
13%	11%	2%	1/2% = 50

In the Stein study, men and women ages 18-65 admitted to the University of California San Diego Level 1 Surgical Trauma Center during a 39 month period between 2001-2004 were recruited to participate in the study. 48 patients volunteered to participate and were randomized to receive either propranolol (n=17), gabapentin (n=14), or placebo (n=17). Medication was administered to subjects within 48 hours of admittance to the trauma center, and once started, subjects were asked to continue the medication for 14 days. Propranolol was started at 20 mg for

3 times daily and uptitrated over 2 days to 40 mg 3 times daily. Gabapentin was started at 300 mg 3 times daily and uptitrated over 2 days to 400 mg 3 times daily. Assessments were conducted by telephone at 1, 4, and 8 months post-injury. The assessments included the Acute Stress Disorder Scale (1 month), the Comprehensive International Diagnostic Interview modules for PTSD, MDD, and Panic Disorder (4 and 8 months), the Center for Epidemiologic Studies Depression Scale (1, 4, and 8 months), and, principally, the Posttraumatic Stress Disorder Checklist-Civilian Version (1, 4, and 8 months). The DSM-IV was used to calculate PTSD rates at 4 months. Results are shown below in Tables 9, 10, and 11.

Table 9: Posttraumatic Stress Disorder Checklist (PCL) Scores at 1, 4, and 8 months, Stein et al. Study

	Gabapentin	Propranolol	Placebo
PCL Score: 1 month	29	28	30
PCL Score: 4 months	26	25	29
PCL Score: 8 months	26	23	21

Table 10: PTSD Rates at 4 Month Follow-Up, Stein et al. Study

	Gabapentin	Propranolol	Placebo
PTSD Rate	20%	25%	25%

Table 11: Absolute Risk Reduction and Number Needed to Treat at 4 Month Follow-Up, Stein et al. Study

CER	EER	ARR	NNT
25%	25%	0	0

DISCUSSION

Propranolol is an often used, safe, widely available, inexpensive generic medication used in the treatment of hypertension, migraine prophylaxis, arrhythmias, and chest pain in the United States[8]. The three randomized, controlled, double-blind studies evaluated the efficacy of propranolol administration following a traumatic event in reducing the incidence of PTSD. While the cumulative results of the studies were inconclusive as to the effectiveness of propranolol in reducing PTSD incidence, the Nugent and Pitman studies demonstrated an observable, albeit small, benefit to using propranolol to reduce PTSD symptomology. In all three studies, small sample sizes limited both the significance of the findings as well as limiting generalizability. The Nugent et al study utilized 29 participants, while the Pitman and Stein studies utilized 45 and 48 participants, respectively. Another indisputable limitation of the studies is the inherent difficulty of recruiting acutely injured and traumatized patients to participate in a randomized study. Further studies are certainly warranted utilizing much larger sample sizes to truly determine the efficacy of propranolol in reducing the symptoms of PTSD.

CONCLUSION

It is inconclusive at this time as to the benefit of using propranolol to decrease the symptoms and prevent the development of PTSD. However, the Nugent and Pitman studies support the clinical feasibility of this hypothesis. It can be said that the future study of this medication and its effect on the development of PTSD symptoms is certainly warranted; it is well documented that propranolol inhibits the actions of norepinephrine, a neurotransmitter that plays an integral role in the consolidation of emotionally charged memories, and the antagonism of this neurobiological mechanism is theorized to play a significant role in the evolution of this

disorder. Continued research should be undertaken with larger sample sizes in order to truly evaluate the efficacy of propranolol and its role in preventing PTSD.

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