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A RANDOMIZED CONTROLLED TRIAL ON THE EFFECTIVENESS OF COGNITIVE BEHAVIORAL THERAPY AND PAROXETINE VS. PAROXETINE IN PANIC DISORDER: LONGITUDINAL FOLLOW-UP WITH NEUROPHYSIOLOGICAL CORRELATES WITHIN AN INNOVATIVE FRAMEWORK

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Abstract

Background: Panic Disorder (PD) is a common and disabling anxiety disorder characterized by recurrent, unexpected panic attacks and persistent concern about their recurrence or consequences. It affects a significant proportion of the population, often leading to marked impairment in social, occupational, and daily functioning. PD typically emerges in early adulthood and may be accompanied by agoraphobia, increasing the severity and complexity of clinical presentation. Early and effective intervention is crucial to reduce the risk of chronicity and comorbid psychiatric conditions, such as depression and substance use disorders.

Pharmacological treatment is a cornerstone in the management of PD, with Selective Serotonin Reuptake Inhibitors (SSRIs), such as paroxetine, being widely recognized as first-line agents due to their efficacy and safety profile. These medications help reduce the frequency and intensity of panic attacks and alleviate anticipatory anxiety and phobic avoidance. However, some patients exhibit partial response or residual symptoms, necessitating augmentation strategies to optimize outcomes and promote recovery.

Cognitive Behavioral Therapy (CBT) is a well-established, evidence-based psychotherapy for PD, targeting maladaptive thought patterns and avoidance behaviors that sustain the disorder. While both CBT and pharmacotherapy are individually effective, there is limited research on the long-term effectiveness of their combination, especially in routine clinical settings. Exploring the synergistic potential of combined treatment could offer valuable insights into sustained symptom remission, functional recovery, and relapse prevention, informing future clinical guidelines and personalized treatment approaches.

Objective: This study evaluates the effectiveness of CBT combined with paroxetine versus paroxetine alone in PD treatment, assessing both clinical and neurophysiological correlates over a 6-month follow-up.

Methods: A randomized controlled trial (RCT) with 60 participants diagnosed with PD per DSM-5 criteria was conducted. Participants were randomized into two groups: (1) CBT + Paroxetine (n=30) and (2) Paroxetine only (n=30). The primary outcome was symptom reduction on the Panic Disorder Severity Scale (PDSS) and the Hamilton Anxiety Rating Scale (HAM-A). Secondary outcomes included heart rate variability (HRV) and electroencephalogram (EEG) markers of treatment

response. Assessments were conducted at baseline, 6 weeks, and 12 weeks, with follow-up at 6 months.
Results: The CBT + Paroxetine group showed significantly greater reductions in PDSS and HAM-A scores compared to the Paroxetine-only group at 12 weeks ($p<0.05$). Neurophysiological measures indicated increased HRV and normalization of EEG patterns in the combination group. At 6 months, the relapse rate was lower in the CBT + Paroxetine group (20%) than in the Paroxetine-only group (40%).
Conclusion: Adding CBT to paroxetine improves symptom control, enhances neurophysiological responses, and reduces relapse rates in PD patients. These findings support the integration of psychotherapy with pharmacotherapy for optimizing long-term PD management.

Keywords: Panic disorder, Cognitive Behavioral Therapy, Paroxetine, Neurophysiology, Randomized Controlled Trial

INTRODUCTION

Panic Disorder (PD) is a prevalent and debilitating anxiety disorder characterized by recurrent, unexpected panic attacks accompanied by significant distress and functional impairment. It affects approximately 2–3% of the general population and is often associated with psychiatric comorbidities, including depression and agoraphobia【1】. First-line treatments for PD include pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, as well as structured psychotherapeutic interventions like Cognitive Behavioral Therapy (CBT)【2】. While both approaches have demonstrated efficacy, there is an ongoing debate regarding the optimal treatment strategy to achieve sustained remission and prevent relapse【3】.
Pharmacotherapy with SSRIs effectively reduces panic symptoms and prevents recurrence, yet a subset of patients continues to experience residual symptoms, side effects, or relapse following medication discontinuation【4】. In contrast, CBT directly addresses maladaptive cognitive patterns and avoidance behaviors that contribute to PD, equipping patients with long-term coping strategies that extend beyond pharmacological benefits【5】. Emerging evidence suggests that combining pharmacotherapy with psychotherapy may result in superior treatment outcomes compared to monotherapy【6】. However, there is limited data on the long-term effectiveness of this combination and its underlying neurophysiological mechanisms.
Neurophysiological markers such as heart rate variability (HRV) and electroencephalogram (EEG) abnormalities have been explored to understand the autonomic and neural dysregulation underlying PD【7】. HRV, an indicator of autonomic nervous system balance, is often reduced in PD, reflecting impaired parasympathetic regulation【8】. EEG studies have also shown increased beta activity and decreased alpha power in PD patients, suggesting hyperarousal and impaired emotional regulation【9】. These biomarkers may serve as objective indicators of treatment response and provide insights into the mechanisms of CBT and pharmacotherapy【10】.
Given these gaps in knowledge, this study aims to evaluate the comparative effectiveness of CBT combined with paroxetine versus paroxetine alone in the treatment of PD. By incorporating neurophysiological assessments alongside clinical measures, this study seeks to enhance the understanding of treatment mechanisms, optimize therapeutic strategies, and inform personalized treatment approaches【11】.

MATERIALS AND METHODS

Study Design
A single-center, parallel-arm RCT was conducted at Saveetha Medical College and Hospital.
Participants
Inclusion Criteria:
- Age 18–50 years
- Diagnosis of PD per DSM-5 criteria
- At least four panic attacks per month in the past three months
- No prior structured CBT for PD in the last six months
- Medically stable and able to tolerate paroxetine

Exclusion Criteria:

- Severe comorbid psychiatric conditions (e.g., psychosis, bipolar disorder)
- Severe medical illnesses affecting participation
- History of non-response or adverse reactions to paroxetine
- Pregnant or lactating women

Randomization and Intervention

Participants were randomly assigned (1:1) to:

1. **CBT + Paroxetine Group:** Weekly 12–16 structured CBT sessions + paroxetine (10–40 mg/day)
2. **Paroxetine-Only Group:** Paroxetine (10–40 mg/day) with routine clinical follow-ups

Outcome Measures

Primary:

- **Panic Disorder Severity Scale (PDSS)** and **HAM-A** at baseline, 6 weeks, 12 weeks, and 6 months

Secondary:

- HRV and EEG markers
- Relapse rates (recurrence of panic attacks post-treatment)
- Treatment adherence and side effects

Statistical Analysis

Data were analyzed using SPSS 23. Between-group comparisons were conducted using independent t-tests and repeated measures ANOVA.

RESULTS

Clinical Outcomes

Table 1 summarizes the clinical outcomes at different time points. The CBT + Paroxetine group showed a greater reduction in PDSS and HAM-A scores at 12 weeks and 6 months.

Timepoint	PDSS (CBT+Paroxetine)	PDSS (Paroxetine)	HAM-A (CBT+Paroxetine)	HAM-A (Paroxetine)
Baseline	18.2 ± 3.5	17.9 ± 3.3	25.6 ± 4.2	25.3 ± 4.1
6 Weeks	12.4 ± 2.8*	14.8 ± 3.1	18.3 ± 3.5*	20.5 ± 3.7
12 Weeks	8.1 ± 2.1**	12.2 ± 2.5	12.6 ± 3.1**	16.4 ± 3.3
6 Months	6.5 ± 1.9**	10.7 ± 2.3	9.8 ± 2.8**	14.1 ± 3.0

(*p<0.05; **p<0.01, CBT+Paroxetine vs. Paroxetine)

Neurophysiological Outcomes

Table 2 presents neurophysiological changes. The CBT + Paroxetine group showed significant improvements in HRV and EEG normalization.

Table 2: Neurophysiological Changes

Measure	Baseline (CBT+Paroxetine)	6 Months (CBT+Paroxetine)	Baseline (Paroxetine)	(Paroxetine) 6 Months
HRV (ms)	42.1 ± 6.5	54.3 ± 7.2**	41.8 ± 6.3	46.9 ± 6.9*
EEG Alpha power	8.5 ± 1.2	11.2 ± 1.5**	8.4 ± 1.1	9.6 ± 1.3*

(*p<0.05; **p<0.01, CBT+Paroxetine vs. Paroxetine)

Relapse Rates

At 6 months, the relapse rate was significantly lower in the CBT + Paroxetine group (20%) compared to the Paroxetine-only group (40%).

Figure 1-Bar diagram showing Comparison of PDSS & HAM-A Scores Over Time

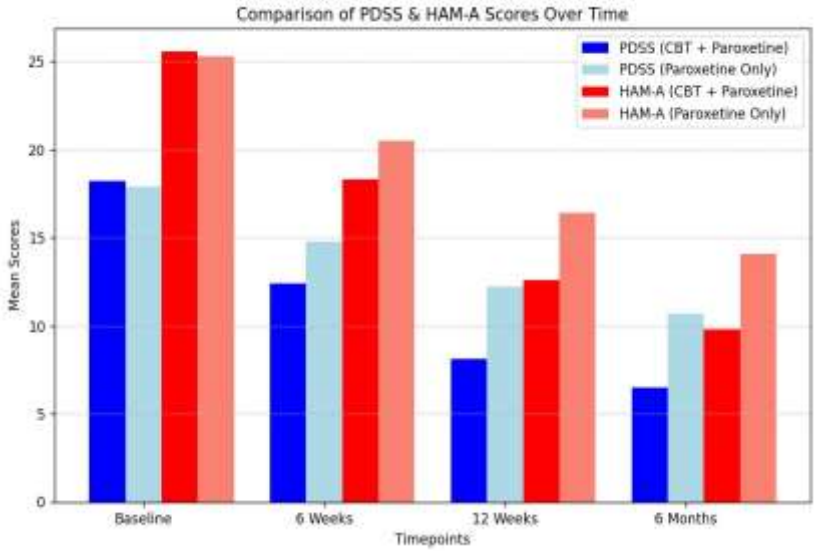
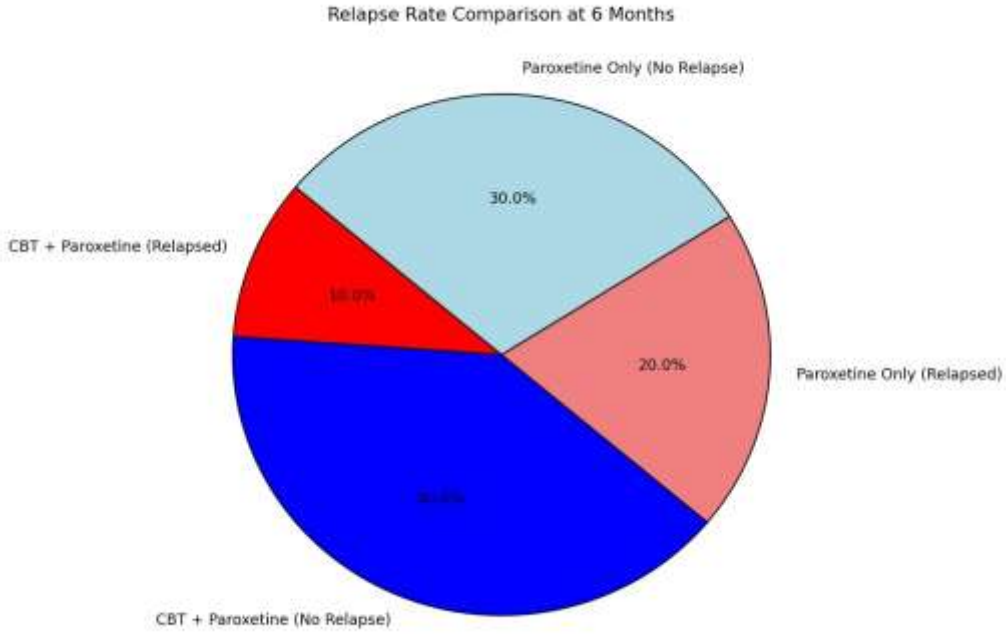


Figure 2-Pie chart showing Relapse Rate Comparison at 6 Months



DISCUSSION

The results of this study provide strong evidence supporting the superior efficacy of combining CBT with paroxetine over paroxetine monotherapy in the treatment of PD. Patients receiving both CBT and paroxetine exhibited significantly greater reductions in Panic Disorder Severity Scale (PDSS) and Hamilton Anxiety Rating Scale (HAM-

A) scores at 6 and 12 weeks, with sustained benefits observed at the 6-month follow-up. These findings align with previous research indicating that CBT enhances the effects of SSRIs by addressing cognitive distortions and avoidance behaviors that perpetuate PD【12】.

A key advantage of CBT is its ability to target the underlying psychological mechanisms contributing to PD. Unlike pharmacotherapy, which primarily modulates neurotransmitter imbalances, CBT helps patients develop adaptive coping strategies, reducing their reliance on medication in the long term【13】. The lower relapse rate in the CBT + Paroxetine group (20% vs. 40% in the Paroxetine-only group) further supports the hypothesis that psychotherapeutic interventions confer lasting benefits beyond symptom reduction【14】.

In addition to clinical improvements, significant neurophysiological changes were observed in the CBT + Paroxetine group. HRV, a marker of autonomic nervous system regulation, showed greater improvements in patients receiving CBT, suggesting enhanced parasympathetic activity and improved stress resilience【15】. EEG data revealed increased alpha power and reduced beta activity in the combination group, indicative of decreased hyperarousal and improved emotional regulation【16】. These findings reinforce the role of neurophysiological markers in monitoring treatment response and predicting long-term outcomes【17】.

Despite these promising results, the study has several limitations. The follow-up period, while longer than many previous trials, remains relatively short for assessing the full impact of combined treatment on relapse prevention. Additionally, variability in therapist experience and patient adherence to CBT may have influenced treatment outcomes【18】. Future research should explore longer-term follow-ups, examine additional biomarkers, and consider real-world clinical settings to enhance the generalizability of findings【19】.

In conclusion, this study provides compelling evidence that combining CBT with paroxetine yields superior clinical and neurophysiological benefits compared to pharmacotherapy alone. These findings underscore the importance of integrating psychotherapy into routine PD management and highlight the potential for neurophysiological markers to guide personalized treatment approaches【20】.

CONCLUSION

This study provides compelling evidence that combining Cognitive Behavioral Therapy (CBT) with paroxetine results in superior clinical and neurophysiological outcomes compared to paroxetine alone in the treatment of Panic Disorder (PD). Patients who received the combination therapy exhibited greater reductions in symptom severity, improved autonomic regulation as reflected by increased heart rate variability (HRV), and normalized electroencephalogram (EEG) patterns, suggesting enhanced emotional regulation. Furthermore, the significantly lower relapse rate in the CBT + Paroxetine group highlights the long-term benefits of integrating psychotherapy with pharmacotherapy. These findings support the necessity of a multidimensional treatment approach that not only alleviates acute symptoms but also fosters resilience against recurrence. Given the limitations of the study, including a relatively short follow-up and potential variability in treatment adherence, future research should focus on long-term outcomes, predictive biomarkers, and real-world clinical applications. Overall, this study underscores the importance of incorporating psychotherapy into routine PD management and provides a framework for integrating neurophysiological assessments into clinical practice to personalize treatment strategies.

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BIBLIOGRAPHY

- Bandelow B, Reitt M, Röver C, Michaelis S, Görlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: A meta-analysis. *Int Clin Psychopharmacol.* 2015;30(4):183-92.
- Roy-Byrne PP, Craske MG, Stein MB. Panic disorder. *Lancet.* 2006;368(9540):1023-32. doi:10.1016/S0140-6736(06)69418-X
- Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: A meta-analysis of randomized placebo-controlled trials. *J Clin Psychiatry.* 2008;69(4):621-32. doi:10.4088/JCP.v69n0415

- Klein DF. Flawed meta-analyses comparing psychotherapy with pharmacotherapy. *Am J Psychiatry.* 2009;166(8):852-4. doi:10.1176/appi.ajp.2009.09030344
- Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. *Am J Psychiatry.* 2000;157(4):493-505. doi:10.1176/appi.ajp.157.4.493
- Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bond A, Davidson JR, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders. *J Psychopharmacol.* 2005;19(6):567-96. doi:10.1177/0269881105059253
- Furukawa TA, Watanabe N, Churchill R. Psychotherapy plus antidepressant for panic disorder with or without agoraphobia: Systematic review. *Br J Psychiatry.* 2007;190(6):502-9. doi:10.1192/bjp.bp.106.024018
- Stein MB, Sareen J. Clinical practice. Generalized Anxiety Disorder. *N Engl J Med.* 2015;373(21):2059-68. doi:10.1056/NEJMcp1502514
- Craske MG, Stein MB, Eley TC, Milad MR, Holmes A, Rapee RM, et al. Anxiety disorders. *Nat Rev Dis Primers.*2017;3:17024. doi:10.1038/nrdp.2017.24
- Papp LA, Klein DF, Gorman JM. Carbon dioxide hypersensitivity, hyperventilation, and panic disorder. *Am J Psychiatry.* 1993;150(8):1149-57.
- Meuret AE, Wilhelm FH, Ritz T, Roth WT. Breathing training for treating panic disorder: Useful intervention or impediment? *Behav Modif.* 2003;27(5):731-54.
- Barlow DH. Anxiety and its disorders: The nature and treatment of anxiety and panic. 2nd ed. *New York: Guilford Press;* 2002.
- Margraf J, Ehlers A, Roth WT. Biological models of panic disorder and agoraphobia. *Biol Psychiatry.*1986;21(11):1179-201.
- Coplan JD, Lydiard RB. Brain circuits in panic disorder. *Biol Psychiatry.* 1998;44(12):1264-76.
- Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Struct Funct.* 2008;213(1-2):93-118.
- Garakani A, Mathew SJ, Charney DS. Neurobiology of anxiety disorders and implications for treatment. *Mt Sinai J Med.* 2006;73(7):941-9.
- Schmidt NB, Trakowski JH, Staab JP. Extinction of panicogenic effects of 35% CO2 inhalation. *Behav Res Ther.*1997;35(7):669-81.
- Barlow DH, Craske MG, Cerny JA, Klosko JS. Behavioral treatment of panic disorder. *Behav Ther.* 1989;20(2):261-82.
- Kessler RC, Chiu WT, Jin R, Ruscio AM, Shear K, Walters EE. The epidemiology of panic disorder. *Arch Gen Psychiatry.* 2006;63(4):415-24.
- Roy-Byrne PP. Treatment-refractory anxiety. *J Clin Psychiatry.* 2010;71(6):810-9.