



Original Article

# Comparative Effectiveness of Pharmacotherapy, Cognitive Behavioural Therapy and their Combination for Depression and Anxiety in Newly Diagnosed Cancer Patients: A 6-week Prospective Observational Study

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## ABSTRACT

**Objectives:** Despite the recent rise in cancer prevalence in India, psychological support is largely ignored. There is very less research on effectiveness of cognitive behavioural therapy (CBT) and pharmacotherapy (PT) as treatment options for psychological distress in cancer patients in India. So, this study was planned to evaluate the relative efficacy of PT, CBT, and their combination in reducing anxiety and depressive symptoms in newly diagnosed cancer patients referred for psychiatric evaluation at a tertiary care hospital in India.

**Materials and Methods:** Between January 2022 and December 2024, newly diagnosed adult cancer patients referred for psychiatric evaluation were enrolled in the study. Of the 456 patients, 32 (6.9%) had a positive screening for generalised anxiety disorder and 75 (16.4%) for major depressive disorder. The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition Disorders, Clinician Version was used to confirm the diagnosis for these patients. Patients selected (1) eight sessions of CBT, (2) selective serotonin reuptake inhibitors (SSRIs) (PT) or (3) both (combination therapy [COMB]). Depression and anxiety severity were assessed using the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A), respectively. The minimal clinically important difference (MCID) was defined as a  $\geq 3$ -point reduction in HAM-D and a  $\geq 2$ -point reduction in HAM-A. A comparison of reductions in scale scores was made at baseline and at 6 weeks.

**Results:** In the depression cohort ( $n = 75$ ), for PT ( $n = 38$ ), CBT ( $n = 19$ ) and COMB ( $n = 18$ ), mean HAM-D change was  $-2.8 \pm 0.7$  (standard error [SE] 0.12, 95% confidence interval [CI] [2.57, 3.03]),  $-0.8 \pm 0.5$  (SE 0.12, 95% CI [0.53, 1.01]) and  $-9.3 \pm 8.9$  (SE 2.10, 95% CI [5.14, 13.36]); baseline-adjusted Analysis of Covariance  $F(2,72) = 48.1$ ,  $p < 0.001$ , partial  $\eta^2 = 0.57$ . COMB exceeded HAM-D MCID in every participant and achieved 33% remission. The mean change in HAM-A ( $n = 32$ ) was  $-3.9 \pm 1.9$  (SE 0.56, 95% CI [2.79, 4.99]) (PT,  $n = 12$ ),  $-3.8 \pm 1.7$  (SE 0.49, 95% CI [2.79, 4.71]) (CBT,  $n = 12$ ) and  $-3.5 \pm 1.4$  (SE 0.50, 95% CI [2.52, 4.48]) (COMB,  $n = 8$ ); the difference between the groups was not significant ( $F(2,29) = 0.54$ ,  $p = 0.59$ ). All arms exceeded the HAM-A MCID threshold; however, response rates ( $\geq 50\%$  reduction) remained  $\leq 13\%$ .

**Conclusion:** Combined PT (SSRI) and CBT showed the most significant improvement in depression symptoms, while all treatment approaches provided comparable relief for anxiety. The study underlines the importance of integrated care in oncology and advocates a combined approach to treating cancer patients with depression and anxiety. Further research is needed to optimise treatments for anxiety, particularly in settings with limited resources.

**Keywords:** Anxiety, Cognitive behavioural therapy, Depression, Palliative care, Psycho-oncology

## INTRODUCTION

Once regarded mainly as a physical illness, cancer is increasingly seen as a bio-psycho-social challenge. After hearing the diagnosis, many patients experience emotions that lead to psychological symptoms matching the pain of tumours. Meta-analyses show that within 12 months of

diagnosis, roughly 20% meet formal criteria for anxiety or depression.<sup>[1]</sup> These overlapping disorders affect adherence to chemotherapy, extend hospital stays, inflate costs and are even linked with earlier death.<sup>[2]</sup>

In India, where new cases have roughly doubled in twenty years, psychosocial support remains the most overlooked

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part of cancer care.<sup>[3]</sup> The European Society for Medical Oncology and the National Comprehensive Cancer Network (NCCN) both urge that drugs or therapy after screening shows distress.<sup>[4,5]</sup> Yet, most supporting studies come from high-income settings, and the same approach falters in India, where trained therapists and reliable psychiatric services are scarce.<sup>[6]</sup> Selective serotonin reuptake inhibitors (SSRIs) are often prescribed because they have few side effects and little interaction with standard chemotherapy.<sup>[7]</sup> Meanwhile, cognitive behavioural therapy (CBT) helps patients reframe distorted thoughts and manage the fear, sadness and uncertainty that follow the diagnosis.<sup>[8]</sup> Global research reports moderate effect sizes for SSRIs and CBT when used alone, and some studies even hint that a combined approach might offer extra value.<sup>[8,9]</sup>

Understanding the minimal clinically important difference (MCID) for rating scales such as the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) is vital if clinicians wish to read results in meaningful terms. Recent investigations propose that a shift of at least three points on the HAM-D and two points on the HAM-A signals a noteworthy change in patients.<sup>[10,11]</sup> When these MCID cut-offs feature in study reports, they equip doctors with a clear yardstick for weighing whether a treatment's gains offset its time and expense, an issue that looms large in clinics with tight budgets.

Prevalence figures for major depressive disorder (MDD) and generalised anxiety disorder (GAD) among cancer patients differ widely, with survey data placing the rate at roughly 18–30%.<sup>[12,13]</sup> However, because most surveys rely on questionnaires rather than full psychiatric evaluations, the real numbers may be either exaggerated or masked. Reliable estimates from structured evaluations can guide planners in deciding how to channel scarce resources into the services of psycho-oncology in low and middle-income countries (LMICs).

Against this backdrop, we conducted a prospective observational study with two primary objectives. First, to estimate the prevalence of MDD and GAD among newly diagnosed cancer patients referred for psychiatric evaluation at an Indian tertiary care centre using gold-standard psychiatric interviews. Second, compare 6 weeks changes in HAM-D and HAM-A scores among patients treated with (i) pharmacotherapy (PT) alone, (ii) CBT alone or (iii) a combination of both.

## MATERIALS AND METHODS

### Study design and setting

This research followed a pragmatic prospective observational cohort model at a large, 1500-bed tertiary care hospital in Western India. During the study period, oncologists consecutively referred newly diagnosed adult cancer patients with suspected psychological distress for psychiatric evaluation, and all such referrals ( $n = 456$ ) were assessed

using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition Disorders, Clinician Version (SCID-5-CV). Approval from the Institutional Ethics Committee was secured before starting the study. Written informed consent was obtained from all participants in their preferred language (Hindi or Gujarati). Participants were assured that declining participation would not affect their oncological care. For those showing signs of psychological distress but not enrolled in the study, referrals were made to the psycho-oncology liaison team as per institutional protocols.

### Sample size and participants

The sample size of 450 participants was obtained by estimating a prevalence of psychiatric morbidity at 20% in newly diagnosed cancer patients<sup>[11]</sup> including screening for and treating clinically meaningful differences in depression and anxiety with an 80% statistical power. The calculation was performed considering the three treatment arms to achieve a significance level of 0.05 and sufficient power to detect medium-to-large effect sizes (Cohen's  $d = 0.5-0.8$ ) for the primary outcomes. A total of 456 patients were finally screened in the study.

Inclusion criteria were (1) histologically confirmed solid malignancy within the preceding 4 weeks, (2) age  $\geq 18$  years and (3) cognitive capacity to complete diagnostic interviews. Exclusion criteria included dementia, major neurocognitive disorders, current psychotic episodes, Eastern Cooperative Oncology Group (ECOG) performance status  $>3$ , ongoing psychotropic treatment or life expectancy  $<8$  weeks, which are contraindications for SSRIs or CBT.

### Data collection

All patients referred for psychiatric evaluation were screened for psychiatric distress using structured clinical interviews conducted by an attending psychiatrist. SCID-5-CV was used for diagnosis confirmation.<sup>[14]</sup> Patients with a primary diagnosis of MDD or GAD were enrolled. Sociodemographic data, cancer stage and ongoing cancer treatment were also collected. We did not administer a standardised physical symptom severity instrument (e.g., pain or global symptom burden scale) beyond using ECOG performance status as part of the exclusion criteria. Symptom severity was assessed using the HAM-D and HAM-A.<sup>[15,16]</sup> Inter-rater reliability for the SCID-5-CV and clinical assessment was validated by a second psychiatrist on 10% of interviews.

### Treatment allocation

The study was conceived as a pragmatic observational cohort intended to reflect the shared decision-making process used in routine psycho-oncology care at the centre, rather than as a randomised efficacy trial. So following SCID-5-CV confirmation of MDD or GAD, the study psychiatrist, often together with the treating oncologist,

provided structured counselling in Hindi or Gujarati about PT, CBT and combination therapy (COMB), including expected benefits, common side-effects and the time and travel requirements for therapy sessions. Patients and, where present, family caregivers were encouraged to ask questions and the treatment modality was chosen through shared decision-making. Three treatment options were (1) PT: Patients received first-line SSRI- fluoxetine, sertraline or escitalopram (only these 3 SSRIs were selected as they are available for free at the study hospital) - dosed at a standardised fluoxetine-equivalent range of 20–30 mg/day in both the depression and anxiety cohorts.<sup>[17]</sup> Clinicians could adjust doses for side effects, and up to 10 mg of nighttime diazepam was permitted to relieve insomnia; (2) CBT: Patients undertook eight structured individual sessions over 6 weeks (approximately one to two sessions per week), each lasting 45–60 min, led by Rehabilitation Council of India-recognised psychologists. Sessions followed a brief, manual-based protocol emphasising psychoeducation about cancer-related distress, behavioural activation, cognitive reframing of illness-related negative automatic thoughts and problem-solving around treatment logistics and role functioning, chosen to be feasible within routine oncology workflows while targeting key cognitive-behavioural processes;<sup>[18]</sup> (3) COMB: Participants in this arm receive both the pharmacologic regimen and the CBT program described above, delivered in parallel whenever feasible.

### Outcome measures

The study's main aim was to document how much anxiety and depression decreased between baseline and week 6, using the HAM-D and HAM-A for measurement. A 6-week follow-up interval was selected because it represents a standard early outcome time-point at which SSRI effects and the impact of an initial CBT course are typically observable, and because a longer mandatory follow-up was not feasible in our setting without substantial loss to follow-up due to treatment schedules and travel burden.<sup>[18,19]</sup> MCID was pre-set as a three-point drop on HAM-D and two-point fall on HAM-A.<sup>[10,11]</sup> Secondary aims tracked full response (at least 50% symptoms reduction), remission (HAM-D score <7 or HAM-A score <7) and any adverse event, with severity scored under CTCAE version 5.0. Adherence to PT was defined as ≥80% of prescribed pills taken, and CBT adherence was defined as attending at least 80% of scheduled sessions. Although originally developed as clinician-rated symptom scales, the HAM-D and HAM-A are widely used as outcome measures in intervention trials for depression and anxiety in medical populations and are sensitive to change over time. In this pragmatic study, they were selected to provide standardised, clinician-administered ratings of symptom severity that could be feasibly integrated into routine oncology workflows.

### Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences version 26.0 (IBM, Armonk, NY) and Microsoft Office 365. Routine descriptive statistics first outline demographic and clinical traits. Continuous variables were compared with one-way Analysis of Variance or the non-parametric Kruskal–Wallis's test, whichever fitted the data. Categorical items were examined through Pearson or Chi-square. Within-group change was analysed by a paired *t*-test. An Analysis of Covariance (ANCOVA) was adjusted for baseline scores then applied for between-group differences in the primary outcome. ANCOVA assumptions were verified: the baseline × group interaction term was non-significant ( $F(2,69) = 1.28, p = 0.29$ ), confirming homogeneity of regression slopes; normality of residuals was assessed using the Shapiro–Wilk test; homoscedasticity was verified using Levene's test and linearity was confirmed by scatterplot inspection. Between-group ANCOVA results are reported with *F*-statistic, degrees of freedom, *P*-value and partial  $\eta^2$  effect size. Baseline-adjusted group means (least-square means) with 95% confidence intervals are reported. To account for multiple pairwise comparisons among treatment groups, the Holm–Bonferroni correction was applied. Both unadjusted and Holm-adjusted *p*-values are reported for all between-group tests.

To give the improvement practical meaning, Cohen's *d* was calculated as the standardised mean change, defined as the mean change score divided by the standard deviation of paired differences, to quantify within-group effect sizes. Finally, multivariable logistic regression sifted predictors of treatment response, including gender, cancer stage (I–II vs. III–IV), therapy type and mean-centred baseline symptom level. Continuous predictors (baseline symptom severity measured by HAM-D or HAM-A) were mean-centred before model fitting to improve interpretability and reduce multicollinearity. Model diagnostics included assessment of variance inflation factors (VIF) to detect multicollinearity, and model fit was evaluated using the Hosmer–Lemeshow goodness-of-fit test with reported degrees of freedom. The logistic regression model reports the intercept ( $\beta_0$ ), sample size, Nagelkerke pseudo- $R^2$  and Hosmer–Lemeshow  $\chi^2$  with degrees of freedom. Statistical significance was set at  $p < 0.05$ , and all tests were two-tailed.

### RESULTS

Between January 2022 and December 2024, a total of 456 adult cancer patients were screened for psychological distress. After screening and clinical interview, 75 patients (16.4%) had MDD and 32 patients (6.9%) had GAD, yielding an overall prevalence of psychiatric disorders of 23.4% ( $n = 107$ ). Of those diagnosed with MDD, 38 patients (50%) selected PT, 19 patients (26%) chose CBT and 18 patients (24%) selected Combined COMB. Among the GAD group,

12 patients (42.9%) received PT, 12 patients (38.1%) engaged in CBT and 8 patients (19%) used the selected COMB. All participants completed a 6-week follow-up.

Table 1 summarises the demographic and clinical characteristics of participants for the MDD cohort, and Table 2 shows the characteristics for the GAD cohort. The mean age across subgroups ranged from 45 to 52 years. The male proportion varied, highest in the CBT-Depression group (77%) and lowest in the PT-Depression (44%). Most participants had advanced-stage (Stage III–IV) cancer and were receiving chemotherapy. Baseline depressive severity (HAM-D) was highest in the COMB-Depression group and lowest in CBT-Depression, while baseline anxiety severity (HAM-A) was similar across arms. The groups did not differ significantly in age ( $F(2,72) = 0.54, p = 0.58$ ), sex distribution ( $\chi^2(2) = 0.49, p = 0.78$ ), cancer stage ( $\chi^2(4) = 2.12, p = 0.71$ ) or chemotherapy status ( $\chi^2(2) = 0.67, p = 0.72$ ).

Table 3 shows that patients in all three treatment groups had statistically significant decreases in HAM-D scores over the 6 weeks followup. Within the COMB group, the average depression score fell markedly and all participants crossed the MCID threshold, with most achieving clinical response and onethird achieving remission. In the PT group, mean scores also declined with a substantial proportion exceeding the MCID and a smaller proportion reaching response and remission, while the CBT group showed the smallest average change, with only a minority achieving clinical response and no remissions. Between-group comparisons adjusted for baseline scores indicated a large and statistically significant overall treatment effect, with COMB performing better than both PT and CBT and PT performing better than CBT on adjusted post-treatment depression levels and pairwise tests. Table 4 shows that all three treatment arms generated decreases that surpassed the MCID measure using HAM-A. The COMB

**Table 1:** Baseline characteristics of the depression cohort by treatment arm ( $n=75$ ).

Variable	PT ( $n=38$ )	CBT ( $n=19$ )	COMB ( $n=18$ )	Test statistics ( $p$ -value)
Age (Mean $\pm$ SD)	50.4 $\pm$ 11.2	44.0 $\pm$ 12.3	46.4 $\pm$ 13.7	$F(2, 72)=1.25,$ $p=0.297$
Male, $n$ (%)	17 (44.0)	15 (76.9)	10 (58.3)	$\chi^2(2)=3.80,$ $p=0.150$
Stage III–IV, $n$ (%)	27 (72.0%)	14 (69.2)	15 (75.0)	$\chi^2(2)=2.26,$ $p=0.322$
Receiving chemotherapy, $n$ (%)	23 (60.0)	11 (53.8)	11 (58.3)	$\chi^2(2)=7.39,$ $p=0.117$
Baseline HAM-D (Mean $\pm$ SD)	16.64 $\pm$ 2.86	10.62 $\pm$ 1.19	18.75 $\pm$ 4.09	$F(2, 72)=27.76,$ $p<0.001$

Values are presented as Mean $\pm$ SD or  $n$  (%). F-statistics are from one-way Analysis of Variance;  $\chi^2$  statistics are from Pearson's Chi-square test. Degrees of freedom: F ( $df_1=2, df_2=$ residual);  $\chi^2$  ( $df=2$ ). PT: Pharmacotherapy, CBT: Cognitive behavioural therapy, COMB: Combined therapy, HAM-D: Hamilton depression rating scale, SD: Standard deviation. Analysis of Variance was used for continuous variables; Chi-square test for categorical variables,  $p$ -value statistically significant at:  $p<0.05$ .

**Table 2:** Baseline characteristics of the anxiety cohort by treatment arm ( $n=32$ ).

Variable	PT ( $n=12$ )	CBT ( $n=12$ )	COMB ( $n=8$ )	Test statistics ( $p$ -value)
Age (Mean $\pm$ SD)	46.8 $\pm$ 13.5	46.9 $\pm$ 16.6	38.2 $\pm$ 5.4	$F(2, 31)=0.62,$ $p=0.552$
Male, $n$ (%)	7 (55.6)	7 (62.5)	8 (100)	$\chi^2(2)=2.56,$ $p=0.278$
Stage III–IV, $n$ (%)	9 (77.8)	9 (87.5)	8 (100)	$\chi^2(2)=1.15,$ $p=0.563$
Receiving chemotherapy, $n$ (%)	1 (11.1)	6 (50.0)	6 (75)	$\chi^2(2)=9.19,$ $p=0.056$
Baseline HAM-A (Mean $\pm$ SD)	11.44 $\pm$ 1.94	9.75 $\pm$ 2.66	9.50 $\pm$ 1.73	$F(2, 7)=1.67,$ $p=0.217$

Values are presented as Mean $\pm$ SD or  $n$  (%). F-statistics are from one-way analysis of variance;  $\chi^2$  statistics are from Pearson's Chi-square test. Degrees of freedom: F ( $df_1=2, df_2=$ residual);  $\chi^2$  ( $df=2$ ). PT: Pharmacotherapy, CBT: Cognitive behavioural therapy, COMB: Combined therapy, HAM-A: Hamilton anxiety rating scale, SD: Standard deviation. Analysis of Variance was used for continuous variables; Chi-square test for categorical variables,  $p$ -value statistically significant at:  $p<0.05$ .

**Table 3:** Six-week change in HAM-D scores and clinical outcomes by treatment arm (depression cohort,  $n=75$ ).

Group (n)	Baseline HAM-D score (Mean±SD)	HAM-D score at Week 6 (Mean±SD)	Mean Difference in HAM-D Score (Δ±SD)	SE	95% CI	Cohen's d	MCID achievement (%)	Response (≥50%) (%)	Remission (HAM-D<7) (%)	Other statistics
PT (38)	16.64±2.86	13.84±2.98	2.80±0.71	0.12	2.57, 3.03	3.93	26 (68)	11 (28)	2 (4)	Between-group ANCOVA: F (2,72)=48.1, $p<0.001$ , partial $\eta^2=0.57$ Baseline-adjusted least-square means (95% CI) for week6 HAM-D: PT: 13.9 [13.0, 14.8]; CBT: 11.2 [10.1, 12.3]; COMB: 10.3 [9.1, 11.5] Pairwise comparisons (unadjusted/Holm adjusted $p$ ) COMB vs. PT: $p<0.001/p<0.001$ , COMB vs. CBT: $p<0.001/p<0.001$ , PT vs. CBT: $p=0.006/p=0.012$
CBT (19)	10.62±1.19	9.85±1.34	0.77±0.53	0.12	0.53, 1.01	1.45	3 (15)	2 (8)	0 (0)	
COMB (18)	18.75±4.09	9.50±4.01	9.25±8.90	2.10	5.14, 13.36	1.04	18 (100)	12 (67)	6 (33)	

Mean change values presented as mean (SD of individual paired differences). SE: Standard error of the mean change ( $SD/\sqrt{n}$ ). 95% CI calculated using  $SE \times 1.96$ . Cohen's d calculated as mean change/SD of paired differences. MCID: Minimal clinically important difference ( $\geq 3$ -point reduction). Paired  $t$ -tests: PT  $t(37)=24.25, p<0.001$ ; CBT  $t(18)=6.32, p<0.001$ ; COMB  $t(17)=4.41, p=0.001$ . Between-group comparisons adjusted for baseline HAM-D scores. ANCOVA assumptions verified: homogeneity of regression slopes (interaction  $p=0.29$ ), normality of residuals (Shapiro-Wilk  $p=0.23$ ), homoscedasticity (Levene's  $p=0.42$ ). PT: Pharmacotherapy, CBT: Cognitive behavioural therapy, COMB: Combined therapy, HAM-D: Hamilton depression rating scale, SD: Standard deviation, CI: Confidence interval, ANCOVA: Analysis of covariance

group ( $n = 8$ ) posted the largest average decrease, yet none reached the benchmark for clinical response or full remission. The PT group ( $n = 12$ ) recorded an average decline; all 12 participants exceeded the MCID, yet only 1 (11.1%) met the clinical-response threshold. Likewise, the CBT group ( $n = 12$ ) showed a mean drop, with all participants exceeding the MCID, but only 2 (12.5%) achieved clinical response. ANCOVA comparisons among groups found no statistically significant difference in effectiveness. Although HAM-A scores fell within each group, the rates of clinical response and remission were statistically indistinguishable across treatments.

Across the entire sample, HAM-D and HAM-A scores correlated strongly at baseline ( $r = 0.67, p < 0.001$ ) and week 6 ( $r = 0.55, p < 0.001$ ), underscoring the frequent co-presentation of mood and anxiety symptoms in oncology. Despite this overlap, the present analyses considered MDD and GAD as separate primary diagnostic cohorts and did not include a distinct analytic subgroup for patients meeting criteria for

both disorders. A multivariable logistic regression model was used to identify predictors of treatment response (at least a 50% drop in HAM-D or HAM-A scores). The model fit the data well (Hosmer-Lemeshow  $\chi^2(8) = 6.1, p = 0.64$ ) and no multicollinearity was detected among predictor variables since all the VIFs were under 1.7.

As shown in Table 5, the model included  $n = 107$  participants with complete covariate data; intercept  $\beta_0 = -1.97$  ( $SE = 0.65, p = 0.003$ ); Nagelkerke pseudo- $R^2 = 0.42$ . Male sex and those receiving COMB therapy compared to PT had higher odds and patients with early-stage cancer (Stage I–II) had lower odds of improvement. Table 5 includes both unadjusted and Holm-Bonferroni adjusted  $p$ -values for multiple comparison testing. On the contrary, each additional score on the baseline levels of HAM-D or HAM-A was associated with lower odds of response. Treatment selection was non-random and influenced by baseline severity and logistical factors (travel distance). A logistic regression model

predicting COMB selection identified: higher baseline severity (odds ratio [OR] 1.18, 95% confidence interval [CI] 1.07–1.31,  $p = 0.002$ ) and travel distance >50 km (OR 0.41, 95% CI 0.19–0.88,  $p = 0.021$ ) as significant predictors. These

**Table 4:** Six-week change in Hamilton anxiety rating scale scores and clinical outcomes by treatment arm ( $n=32$ ).

Group (n)	Baseline HAM-A Score (Mean±SD)	HAM-A Score at Week 6 (Mean±SD)	Mean Difference in HAM-A Score (Δ±SD)	SE	95% CI	Cohen's d	MCID Achievement	Response (≥50%)	Remission (HAM-A <7)	Other statistics
PT (12)	11.44±1.94	7.56±1.94	3.89±1.95	0.56	2.79, 4.99	1.99	12 (100%)	1 (11.1%)	0 (0%)	Between-group ANCOVA: $F(2,29)=0.54$ , $p=0.59$ , partial $\eta^2=0.04$ (no significant difference) Baseline-adjusted least-square means (95% CI) for week6 HAM-A: PT: 7.7 [6.7, 8.7]; CBT: 6.5 [5.4, 7.7]; COMB: 6.2 [4.9, 7.5] Pairwise comparisons (unadjusted/Holm-adjusted $p$ ) for week6 HAM-A (all non-significant): COMB vs. PT: $p>0.20/p>0.20$ ; COMB vs. CBT: $p>0.20/p>0.20$ ; PT vs. CBT: $p>0.20/p>0.20$
CBT (12)	9.75±2.66	6.00±1.60	3.75±1.70	0.49	2.79, 4.71	2.21	12 (100%)	2 (12.5%)	0 (0%)	
COMB (8)	9.50±1.73	6.00±0.82	3.50±1.41	0.50	2.52, 4.48	2.47	8 (100%)	0 (0%)	0 (0%)	

Mean change values presented as mean (SD of individual paired differences). SE: Standard error of the mean change ( $SD/\sqrt{n}$ ). 95% CI calculated using  $SE \times 1.96$ . Cohen's d calculated as mean change/SD of paired differences. MCID: Minimal Clinically Important Difference ( $\geq 2$  point reduction). Paired  $t$ -tests (within-group): PT  $t(11)=6.90$ ,  $p<0.001$ ; CBT  $t(11)=7.64$ ,  $p<0.001$ ; COMB  $t(7)=7.00$ ,  $p=0.006$ . Between-group comparisons for week 6 HAM-A adjusted for baseline HAM-A. ANCOVA assumptions were assessed and found to be adequately met (linearity, homoscedasticity, normality of residuals and homogeneity of regression slopes). PT: Pharmacotherapy, CBT: Cognitive behavioural therapy, COMB: Combined therapy, SD: Standard deviation, CI: Confidence interval, ANCOVA: Analysis of covariance, HAM-A: Hamilton anxiety rating scale

**Table 5:** Predictors of treatment response at week 6 (multivariable logistic regression,  $n=107$ ).

Predictor	Adjusted OR	95% CI	$p$ -value	Adjusted $p$ -value*
Male sex	1.57	1.01–2.46	0.045	0.090
Early-stage cancer (I–II)	0.72	0.57–0.91	0.009	0.027
CBT vs. PT	0.62	0.38–1.03	0.068	0.136
COMB vs. PT	1.79	1.08–2.97	0.023	0.046
Baseline severity (per-point increase)**	0.94	0.87–1.01	0.091	0.091

\*Holm-Bonferroni adjusted  $P$ -values shown. \*\*Continuous predictor (baseline severity) mean-centred before analysis. Results of multivariable logistic regression identifying predictors of treatment response (defined as  $\geq 50\%$  reduction in HAM-D or HAM-A scores). Factors included sex, cancer stage, treatment modality and baseline severity. OR with 95% confidence intervals are presented. PT: Pharmacotherapy, CBT: Cognitive behavioural therapy, COMB: Combined therapy, OR: Odds ratio, CI: Confidence interval,  $p$ -value statistically significant at:  $p<0.05$ .

variables were included as covariates in outcome analyses to reduce confounding by indication. Sensitivity analyses were conducted to assess robustness of findings: (1) Unadjusted change-score analysis, (2) propensity score adjustment for treatment selection and (3) inverse probability weighting (IPW). Results remained consistent across all approaches, with COMB showing superior outcomes (IPW-adjusted  $p = 0.004$ ), although effect sizes were slightly attenuated after adjustment, supporting robustness of findings.

Adherence to treatment remained uniformly high; both the PT and COMB arms achieved median pill counts of 92% (IQR 89–97%), while CBT attendees completed an average of 6.9 of 8 sessions, equivalent to 86%. Routine safety monitoring identified no serious adverse events. Two individuals in the PT group reported grade 1 nausea linked to fluoxetine, and one participant in the CBT arm experienced brief emotional distress that was resolved without stopping treatment.

## DISCUSSION

This study provides important insight into the best treatment of depression and anxiety in newly diagnosed cancer patients in India, comparing PT, CBT and a combination of both (COMB). Our results show that the COMB works best for depression, points to mixed benefits for anxiety and offers feasible ways for hospitals with limited resources to integrate these tools into their routine care.

This study found that 107 (23.4%) of newly diagnosed cancer patients met full criteria for either MDD or GAD. This prevalence is in the same 20–30% range reported by large global reviews of oncology samples, underscoring a similar burden across different health systems.<sup>[1,12,13]</sup> The rate signals an urgent need for regular screening and prompt treatment in oncology units, especially in LMIC such as India, where mental health funding and services remain scarce.<sup>[3]</sup> Because we relied on structured clinical interviews rather than simple forms, our estimate avoids the common mistakes of counting too many or too few cases. The difference stresses that face-to-face assessment is vital for planning budgets and services in psycho-oncology.

Our study shows that treating depression with a combination of SSRI and CBT outperforms each treatment alone. These results are in line with earlier work documenting the added gains that arise when serotonergic medication is paired with psychotherapeutic effort.<sup>[8,9]</sup> The superior performance of the combined approach in our cohort is biologically and psychologically plausible. PT with SSRIs may lessen negative effects, physiological arousal and information-processing biases, thereby reducing the overall “load” of depressive symptoms. In parallel, CBT directly targets negative automatic thoughts and maladaptive coping patterns that are common in cancer, such as catastrophic predictions about prognosis, hopelessness about treatment and withdrawal from valued roles. When used together, these “bottom-up”

neurobiological effects and “top-down” cognitive-behavioural changes may act synergistically, allowing patients to engage more fully with therapy and to sustain gains beyond the initial pharmacological response.<sup>[20,21]</sup> This method can be implemented in settings with limited resources, as the SSRIs are widely available and the treatment can be integrated into routine care once the staff has received initial training. The strong response in the COMB study is particularly remarkable, as the patients in our study entered treatment with a degree of depression that would be considered severe in many Western studies. This finding suggests that the combination of medication and structured evidence-based treatment can yield significant benefits even when the initial symptoms are severe, which supports integrated care models in similar populations. These findings echo the results of large network meta-analyses which suggest that paired therapy is generally superior to single treatment in depressed patients.<sup>[22]</sup> However, the limited number of COMB groups means that larger multi-centre studies are needed before these conclusions can be accepted.

Significant reductions in depressive symptoms were observed in the PT group, with 68% exceeding the MCID and 28% meeting the clinical response criteria. The high magnitude of the effect highlights the strong antidepressant effect of SSRIs in this population and reinforces their role as a first-line treatment for patients with cancer who are depressed. However, the low 4% remission rate suggests that SSRIs, although useful for symptom relief, rarely provide complete and durable control of cancer-related depression. Similar research shows that any single method, and especially medications alone, is often inadequate to address the complex emotional turmoil that comes with a cancer diagnosis and treatment.<sup>[8]</sup> Therefore, even if PT brings significant benefits, it may not be a strategy that ensures lasting improvements compared to a combination with CBT.

Although the CBT arm produced the smallest mean decrease in depressive scores, it must be remembered that CBT remains a gold-standard option for easing illness-related distress. The modest effect seen here could stem from the intervention lasting only eight sessions spread over 6 weeks or from the higher baseline severity of depression within our sample. Previous research indicates that longer or more bespoke cognitive-behavioural protocols, designed specifically for the stressors that accompany cancer, typically produce stronger gains.<sup>[8]</sup> The limited clinical response noted in the CBT arm therefore underscores the necessity of tailoring treatment and possibly extending session frequency or duration when working with patients who present with moderate-to-severe depression.

In patients with GAD, anxiety scores improved consistently across all three treatment arms, with each arm surpassing the MCID. But between-group testing revealed no statistically meaningful divergence in symptom reduction; the data imply that PT, CBT and their combined protocol furnish comparable

short-term relief for anxiety in cancer survivors. Our results echo earlier work showing that both PT and CBT help reduce GAD among cancer patients, yet the modest rates of meaningful improvement in our cohort hint that this population may need longer or more intensive treatments.<sup>[22-24]</sup> The lack of full remission underscores the complex web of anxiety sources, uncertainty about treatment, worry about prognosis and fear of recurrence, suggesting that interventions must be tailored or extended to reach deeper levels of relief.<sup>[25]</sup>

Multivariable logistic regression pointed to male sex and the use of combined therapy as key predictors of a positive response. Patients with early-stage cancer had lower odds of response compared to advanced-stage disease, possibly reflecting a higher psychological burden in patients with advanced malignancy leading to greater symptom reduction with intervention or differences in baseline severity and care-seeking behaviour. These factors corroborate past studies linking gender and disease stage to levels of psychological distress in oncology patients.<sup>[26,27]</sup> The stronger odds associated with COMB further highlight the value of pairing SSRIs with CBT, especially for individuals whose depressive symptoms are more severe or intricate. Likewise, the finding that higher baseline severity relates to poorer outcome aligns with dose-response patterns seen in other depression research.<sup>[28]</sup>

### Study strengths and limitations

The consecutive recruitment and pragmatic allocation of treatment, which simulates a real clinical scenario where patients select their treatment method, increases the external validity of the study. SCID-5-CV interviews conducted by a psychiatrist minimise the risk of misclassification associated with self-reported screening tools. Adherence to CBT sessions exceeded 85%, while adherence to PT (number of pills taken) averaged 92%. Full 6-week follow-up reduces bias due to differential discontinuation, a common limitation of many studies in the field of psycho-oncology. The use of MCID links statistical significance to clinically relevant changes, which improves practical relevance for practitioners. This study has its own limitations, like the non-random allocation of patients to different treatment groups. Treatment allocation was influenced by patient preference, travel burden and oncologist recommendation, creating potential confounding by indication. Patients opting for combined therapy had higher baseline symptom severity (OR=1.18,  $p = 0.002$ ), suggesting that sicker patients preferentially selected COMB. Although statistical adjustments for treatment selection of predictors and propensity score methods were employed, residual confounding cannot be entirely excluded. Post-hoc power analyses showed the MDD subgroup ( $n = 75$ ) had approximately 60-70% power to detect medium effects, while the GAD subgroup ( $n = 32$ ) had <40% power, limiting the generalisability of findings to the anxiety cohort. Future multisite trials should incorporate randomisation or at least inverse-probability weighting.

Although depressive and anxiety symptoms frequently co-occurred, we did not conduct separate analyses for patients with formal comorbid MDD and GAD, and future work should examine such mixed presentations explicitly. Although the study site serves four neighbouring states, generalisability to rural or private-sector hospitals remains uncertain being a single centre of study. The GAD anxiety subgroup had a small combination arm ( $n = 8$ ); the large effect size observed may be unstable due to small sample size and requires replication in larger studies. Six weeks may underestimate the full trajectory of antidepressant benefits and provide insufficient time to assess relapse. This relatively short horizon reflects pragmatic feasibility rather than an assumption that 6 weeks captures the full course of therapeutic benefit. So, Future studies should extend follow-up to 24 weeks. In addition, we did not systematically assess physical symptom burden with validated scales, which limits our ability to relate psychological outcomes directly to pain or other somatic symptoms; future studies should include structured measures of symptom burden and quality of life. Factors such as financial constraints, perceived social support and health literacy were not assessed but may influence treatment response. Another limitation is that the CBT component was not accompanied by formal session-wise process measures. We did not systematically record changes in negative automatic thoughts, homework adherence or within-session shifts in coping strategies. Given the strong theoretical emphasis on cognitive restructuring and behavioural activation in CBT, future studies should incorporate structured tools to document session-level processes and to classify common cancer-related themes (for example, fear of recurrence, concerns about body image or perceived burden on family). The study also did not evaluate the impact of both cancer and psychological distress on quality of life, which should be done in future studies.

### Clinical implications

These findings support a stepped-care pathway for Indian comprehensive cancer centres: (1) Screen all patients using a validated ultra-short tool (e.g., NCCN Distress Thermometer), (2) assess positive screens through psychiatrist-administered interviews to distinguish adjustment reactions from diagnosable MDD or GAD, (3) Treat moderate-to-severe depression with combined SSRI+CBT when therapist availability allows; offer PT alone in resource-limited settings, (4) Manage GAD with either treatment initially; reassess at 8 weeks and escalate to combination therapy or extended CBT if the HAM-A score remains  $\geq 7$  or below the MCID threshold.

### CONCLUSION

The study highlights the importance of integrating interventions and organised psychiatric evaluation into cancer care in LMICs like India. Both statistical analysis and MCID support positive

results with combined CBT-PT treatment for depression, which confirms its clinical relevance and applicability in cancer treatment. Our findings also suggest that providing mental health support with empathy and integrating it into routine cancer care makes patients more receptive to treatment. The lack of significant differences in anxiety outcomes between groups suggests the need for more targeted or longer-term interventions, especially in the oncology population, for GAD. These results call for further research into adaptive, step-by-step models of treatment that respond to the complexity and context of symptoms. By addressing the important gap in evidence in low-resource settings, the study provides a basis for the expansion of psychiatric services in oncology and for the mainstreaming of mental health as a standard part of comprehensive cancer care.

**Ethical approval:** The research/study was approved by the Institutional Review Board at Sumandeep Vidyapeeth Institutional Ethics Committee, approval number SVIEC/ON/Phar/BNPG20/D21038, dated 1st December 2021.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given consent for clinical information to be reported in the journal. The patient understands that the patient's names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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