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A Brief Comparison Between Psychosocial Intervention and Pharmacotherapy for Patients with Bipolar Disorder and Effect on Their Clinical Outcomes

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ABSTRACT

Background: Bipolar affective disorder causes fluctuating mood and functional impairment; while medication is central, structured psychosocial therapy like IPSRT may enhance outcomes, with evidence from low-resource settings, especially India, still limited.

Aim: To assess the efficacy of adjunctive IPSRT in people with BPAD taking pharmacotherapy compared to pharmacotherapy alone.

Methods: In this prospective, comparative, pre-post study, 82 persons with BPAD (as per DSM-V) were randomised to the two groups (n = 41 each). The intervention was 12 weeks long in psychiatric hospital at Ahmedabad. Outcomes assessed were depressive symptoms (HAMD-17), manic symptoms (YMRS), functional disability (WHODAS 2.0), and systemic inflammation (CRP), which were measured at baseline, 6 weeks, and 12 weeks.

Results: Both groups were comparable in sociodemographic characteristics, and adjusted analyses accounted for baseline variations in clinical measures. At 3 months, the experimental arm showed significantly greater improvement in depression (HAMD-17: 19.75 → 12.00; $p < 0.001$) and mania (YMRS: 18.24 → 12.37; $p < 0.001$) than controls ($p < 0.05$). Functional disability decreased substantially (WHODAS: 78.56 → 55.11; $p = 0.048$), and CRP levels were significantly reduced (12.05 → 8.26 mg/L; $p = 0.031$) in the experimental group. Control group changes were modest. Gender and age subgroup analyses indicated uniform benefits, though middle-aged participants showed a trend toward more consistent improvements.

Conclusion: IPSRT, when combined with pharmacotherapy, produces superior outcomes in mood stabilization, functional recovery, and reduction of systemic inflammation in BPAD compared to pharmacotherapy alone. These findings support IPSRT as an effective, holistic adjunctive treatment, potentially addressing both psychosocial and biological aspects of bipolar disorder.

Keywords: *Bipolar affective disorder, Interpersonal and Social Rhythm Therapy, Mood stabilization, Functional recovery, Inflammation, Efficacy.*

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1. INTRODUCTION

Bipolar affective disorder (BPAD) is a chronic mental condition that can be diagnosed in more than 40 million individuals around the world, and the lifetime prevalence rates range between 0.5% and 1% (1,2), and an increasing public health challenge in India (1). National surveys in India indicate high levels of functional disability in adults with bipolar disorder in the working-age category with high levels of relapse, treatment drop-out, and high rates of suicide which are about one in every five cases (3,4). It affects the economy as well, causing loss of productivity, stressing out the caregivers, and leading to more hospitalization (5).

Although the core of care is medication, it does not turn out to be a solution to persistent symptoms or the restoration of fully functioning and therefore the importance of structured and evidence-based psychosocial measures is emphasized. including IPSRT. The use of pharmacology in the treatment of BPAD still remains the focal point of treatment, with lithium, the most prevalent agent, reducing manic and depressive symptoms as well as cutting suicide risk by more than half (6). Valproate, lamotrigine and atypical antipsychotics (quetiapine and olanzapine) are other agents commonly used (7,8). Nevertheless, drugs are usually not enough to achieve stability or functional recovery over a long period of time. Several adjunctive psychosocial options are suggested in major treatment guidelines, and they include CBT, family-focused therapy, psychoeducation, and IPSRT (8,9). Such methods lead to better compliance, less relapse and address interpersonal and circadian imbalances (9). IPSRT deals with mood instability through the encouragement of regular daily rhythms and the enhancement of interpersonal skills. Although it is now listed as a third-line adjunct, it has potential as an intervention in patients who have recurrent episodes or who have poor social rhythm regulation (8). The addition of psychosocial therapies to usual care, especially in low-resource are a potential to benefit not only clinical outcomes but also functional recovery, something that goes beyond symptom management (10,11).

Medication, combined with psychosocial interventions, has been reported to be associated with more than mood stabilisation, such as cognitive, functional and even biological ones. Ott and colleagues (12) randomly assigned and tested a group of individuals with remitted bipolar disorder and cognitive deficits using the Action-Based Cognitive Remediation (ABCR). The study was a randomised controlled trial. ABCR showed temporary benefits of executive functioning and perceived cognitive skills, but their effects did not persist. Valls and colleagues (13) also tested an integrative treatment by using psychoeducation, mindfulness, and functional remediation, finding that there were enormous improvements in functioning and depressive symptoms. The AWARE multimodal intervention, which is aimed at functional recovery, was proposed by Schwarz et al. (14), but the outcomes are yet to come. According to Carracedo-Sanchidrian et al., there were significant differences (based on cognitive performance measures) between Mindfulness-Based Cognitive Therapy (MBCT) and psychoeducation when it comes to cognitive performance and brain-derived neurotrophic factor (BDNF) concentrations (15). According to Rotenberg and colleagues (16), the metacognitive training reduced the latency in emotion recognition, but not significantly improved overall performance or quality of life. Kavitha and group (17) found out that a family-focused intervention led by a nurse was able to significantly enhance functioning in symptomatic inpatients with bipolar disorder. Nambiar and co-authors (18) concluded that short term CBT in remission produced a positive effect in reducing depressive and anxiety symptoms and enhanced treatment adherence but not in functional improvements.

With such a scope, the current research can be placed to fill some of the central gaps in the literature. Whereas medication forms the basis of bipolar disorder treatment, it may at many times be inadequate to prevent relapse, reduce residual symptoms or loss of full functioning capacity (10,11). IPSRT and other psychosocial treatments are effective in enhancing treatment outcomes because they focus on circadian stability, interpersonal skills and emotional regulation (19). There is however limited research that has assessed the IPSRT in India and minimal research that has involved the use of biologically based measures (e.g., systemic inflammation markers, e.g., C-reactive protein (CRP) to reflect its wider implications (20)

The aim of this randomised controlled trial was to determine whether structured IPSRT in combination with medication is superior to medication alone. The biopsychosocial approach was used to study the depressive and manic symptoms, functional impairment, and inflammatory markers in a multidimensional perspective. The fact that the study is done in a typical tertiary psychiatric care facility is contextually relevant evidence to prove the need to incorporate IPSRT into standard care protocol.

2. METHODS

2.1 Study Design and Setting

This was a prospective, comparative, pre–post study design that took place in psychiatric clinics across Ahmedabad, Gujarat, India during three months. The Institutional Ethics Committee approved the study protocol, and all the participants gave informed consent.

2.2 Ethical Considerations

The Independent Ethics Committee (ACEAS -Independent Ethics Committee, Ambawadi, Ahmedabad, Gujarat IEC#20SBBS3010001, dated 29th July 2023) reviewed and approved the study protocol before it could be set in motion. Information regarding the purpose, procedures, potential risks and benefits of the study were explained to all participants in detail. Each participant, prior to their enrolment, provided written informed consent as prescribed by the ethical principles identified in the Declaration of Helsinki. The participants were guaranteed that their personal health data will be kept confidential and they were given the freedom to leave the study any time without it affecting their further clinical treatment. All the information gathered was anonymised and it remained purely utilised in research.

2.3 Participants

Participants were purposively recruited from outpatient and inpatient psychiatric services.

Inclusion Criteria

The criteria used to select participants who would take part in the study was that they were adults aged 18-59 years who had a clinical diagnosis of BPAD according to DSM-5 criteria and coded F31.2 (International Classification of Diseases, 10th Revision; ICD-10) (21). Other requirements were that they must be able to give informed consent and be willing to accept the study procedures. The intervention protocol also required willingness to attend structured sessions of psychosocial therapy among the participants who were in the experimental group.

Exclusion Criteria

The study excluded patients who had comorbid psychiatric diagnoses (schizophrenia, schizoaffective, or substance use disorders). There were also those with known organic brain syndromes or intellectual disabilities excluded since it is feared that they may not be able to participate fully in the therapeutic process. Pregnant or lactating women and those using acute injectables cases were excluded. Additional exclusion criteria were the presence of other enrolment in other psychotherapeutic programmes or the existence of severe medical conditions that would require hospitalisation, which would extend to the interventions or confound the outcomes.

Sample Size Calculation

The required sample size was estimated for a two-arm comparison (IPSRT + pharmacotherapy vs. pharmacotherapy alone), assuming a two-sided significance level of 0.05, statistical power of 80%, and equal group allocation. Estimates of group means and standard deviations were drawn from prior literature (22) using GAF as the primary outcome, indicating an expected mean difference of approximately 5 points with a pooled variance of about 113. On this basis, the minimum required number of participants was 34 per arm. To account for an anticipated attrition rate of around 20%, the target was increased to 41 participants in each group (total N = 82), which was successfully achieved in the study.

2.4 Randomisation, Allocation, and Blinding

Participants were randomly assigned to two groups, namely, the experimental group consisting of pharmacotherapy combined with IPSRT versus the control group with pharmacotherapy only. Allocation concealment was provided by means of using sequentially opened opaque envelopes. The random sequence was generated using a computer-based random number generator with simple randomisation. Allocation concealment was maintained with sequentially numbered, opaque, sealed envelopes prepared by an independent researcher not involved in recruitment or assessment. There were no differences between the intervention and control group with regard to age, gender, education, occupation, socioeconomic status, anthropometric measures at baseline. The participants and therapists could not be blinded because of the nature of psychosocial intervention. Nevertheless, in order to reduce the possibility of assessment bias, the whole range of clinical and functional outcome measurements was performed by blinded independent raters who were not informed about the group assignment. These assessors did not participate in the implementation of the intervention and were advised not to talk to the participants about its treatment. An attempt was made to maintain the integrity of blinding during the process of data collection.

2.5 Intervention Protocol

Pharmacotherapy (Both Groups)

They were all given standard psychiatric treatment which included mood stabilisers (e.g. Lithium, valproate), atypical antipsychotics and antidepressants as per clinical indication. Medication adherence was monitored during follow-up visits.

Table 1. Medication usage per study group

Medication used	Group		Total	Pearson chi-square	p-value
	Experimental group	Control group			
Antidepressants	13	12	25	2.456	0.482

Antipsychotic	18	13	31
Lithium	4	8	12
Mood Stabilizer other than lithium	6	8	14

Control Group

Received pharmacotherapy only.

IPSRT (Experimental Group Only)

The experimental group received the administered intervention in a structured, manualised format which began as a treatment programme to treat BPAD developed by Frank and group (19). The group underwent 12 weekly IPSRT sessions over a three-month time interval, structured across four phases (initial, reorganisation, maintenance, and final), and these sessions were conducted by trained psychiatric professionals**.** Each session lasted approximately 45 to 60 minutes. The intervention included some of these core elements: social rhythm monitoring, where the patients completed rhythm charts to stabilise their daily routines including sleep-wake cycles, mealtimes, and social interactions; interpersonal problem-solving, which aimed at solving problems like grief, role transitions, interpersonal conflicts, and interpersonal deficits; and psychoeducation to enhance medication compliance, which included the need to be consistent with pharmacological treatment. Also, the sessions involved stress management and coping techniques to determine the presence of maladaptive responses and promote adaptive coping with the effects of emotions and situations. The sessions of IPSRT were culturally and linguistically modified and the treatment mode focused more on the setup of goals jointly to assist the patients in engaging in treatment and adherence. IPSRT does not only focus on decreasing the acute symptomatology, but also on eliminating the relapse through addressing the psychosocial and circadian vulnerabilities that are common in BPAD.

2.6 Outcome Measures

The assessments were carried out with three time points, which were: at baseline, six weeks, and 12 weeks.

Depression Scale

Depressive symptoms were measured by a 17-item Hamilton Depression Rating Scale (HAMD-17) which is a clinician-rated scale invented by Max Hamilton in 1960s (23) to measure the severity of depression. The scale tests an extent of symptom domains such as mood, guilt, suicidality, insomnia, psychomotor change, anxiety and somatic complaints. The items are rated either 3-point (02) or 5-point (04) scale and provide a total score of 0 to 52 points with higher scores representing more severe symptoms. The conventionally utilized cut-offs of interpretation include: 0-7 (normal ranking), 8-13 (mild), 14-18 (moderate), 19-22 (severe) and 23 and above (very severe depression). The HAMD-17 has no predefined subscales, but the instrument is commonly divided into clusters which approximate core mood symptoms, sleep disturbance, and somatic-anxiety characteristics. It is very common in clinical trials as it is sensitive to change.

Manic scale

Manic symptoms were evaluated on the basis of the Young Mania Rating Scale (YMRS), which is a clinician-rated scale that was designed by Young and colleagues in 1978 (24) to measure the level of manic episode. The YMRS is a 11-item questionnaire which measures mood, motor activity, sexual interest, sleep, irritability, speech, language-thought disorder, content, disruptive or aggressive behaviour, appearance, and insight. The potential of the four items (irritability, speech, thought content and disruptive behaviour) to be more variable results in the scoring of these items on a 0 to 8 scale whereas the others are assessed on a 0 to 4. Scores can be as high as 60 or as low as 0 and the higher the score the more severe the symptoms of mania. There are no universal accepted clinical cut-offs, but scores of greater than 20 suggest moderate to severe mania. One of the reasons the YMRS is popular in the clinical and research contexts is its brevity, reliability, and sensitivity to change.

Disability Scale

The World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) was used to determine functional disability; this is a standardised measurement tool by the Üstün and group in 2010 (25) by the WHO in its International Classification of Functioning, Disability and Health (ICF). WHODAS 2.0 is used to measure the health-related functioning in 6 areas: cognition, mobility, self-care, getting along with people, life activities, and participation in society. In this study, the 36-item version was employed and each of the items was scored using a 5-point Likert scale with the option of 0 (no challenge at all), to 4 (very hard or unable to do). The raw scores are converted into a 0-100 disability scale by using a complex scoring algorithm. WHODAS 2.0 has cross-cultural validation and can be used by various physical and mental health conditions. It has shown good psychometric qualities such as internal consistency, test-retest reliability and sensitivity to change.

Biomarker for Systemic Inflammation

The levels of systemic inflammation were measured by CRP, a well-recognised acute-phase biomarker that is produced by the liver in reaction to pro-inflammatory cytokines, especially interleukin-6 described by Fernandes et al. (26). Higher CRP

has increasingly been used in the pathophysiology of mood disorders such as BPAD and is believed to indicate neuroinflammatory activity. In the study, assays were used to detect low-grade inflammation by using high sensitivity CRP (hs-CRP) assays. Fasting blood samples were taken and analysed in the institutional biochemistry laboratory by standardised immunoturbidimetric procedures. The CRP levels were measured in mg/L, and those with higher levels represented more systemic inflammation. Although rates of normal hs-CRP range between <1.0 mg/L, those >3.0 mg/L are deemed to represent high inflammatory load and increased cardiovascular or psychiatric risk. Recent studies also indicate that CRP levels might also change with mood state in BPAD, whereby, it rises during manic and depressive states and falls during remission.

2.7 Statistical Analysis

Demographic and clinical characteristics were summarised with the aid of the descriptive statistics (mean, standard deviation, frequency distributions). Between-group comparisons were at baseline using chi-square tests and independent samples t-tests. In case of the outcome measures, paired t-test and repeated-measures ANOVA were employed to assess the within-group changes across the time. Independent t-tests were carried out between-groups at 6 weeks and 12 weeks. The analysis was done both using per-protocol and intention-to-treat protocols. The missing data was handled using both last-observation-carried-forward method of handling missing data. The results obtained from intention-to-treat analysis have been used for scientific interpretation. Differential effects were also investigated via subgroup analysis based on gender and age (21 to 30, 31 to 40, 41 to 50 and 51 to 60 years). A p-value <0.05 was considered statistically significant. Data analysis was conducted using SPSS version 25.

3. RESULTS

The recruitment of 82 participants fulfilling the eligibility criteria was conducted and randomized into the experimental (n = 41), receiving IPSRT together with pharmacotherapy, and the control (n = 41) groups that received pharmacotherapy. Randomisation ensured equal allocation. Seventy-nine the participants completed the 3 months intervention and follow-up and there was 96% retention in the two groups. The participant flow has been depicted in Figure 1. The reasons for dropping out for the three participants (one in the experimental group and two in the control groups) have been shown in the diagram. The two groups were statistically matched at baseline on important sociodemographic variables, shown in Table 2.

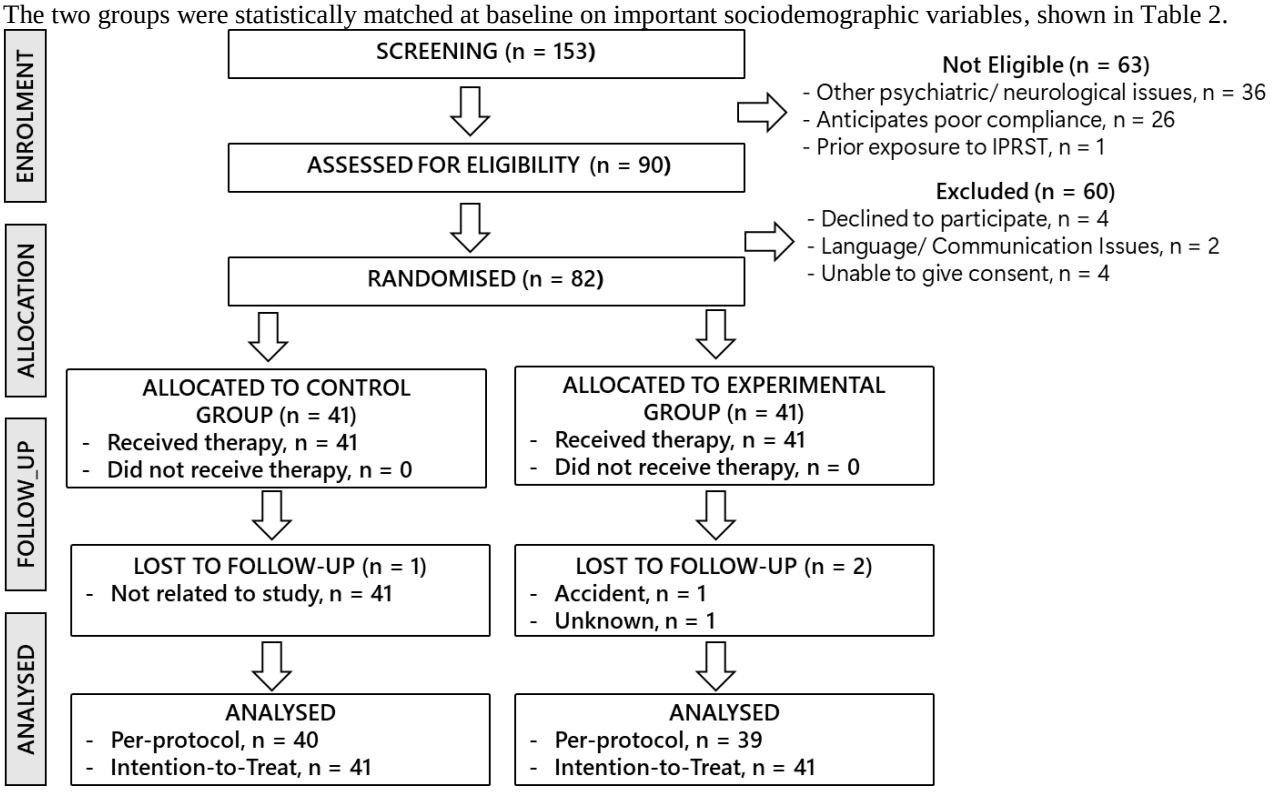

Figure 1. CONSORT (2010) Flow-Diagram

Baseline sociodemographic and clinical characteristics of participants in the intervention and control groups are summarized in Table 2. The two groups were broadly comparable in terms of age, sex distribution, body mass index, marital status, religion, dietary habits, and family type, with no statistically significant differences observed. Educational status and socio-economic class distributions showed minor variations between groups ($p = 0.061$ and $p = 0.130$, respectively), but these did not reach statistical significance and were therefore unlikely to bias the primary outcomes.

Overall, randomization achieved good balance between the two study arms, supporting the internal validity of subsequent comparisons.

Table 2. Demographic variables

Time Point	Experimental Group	Control Group	Between Group
	Mean ± SD	*Mean ± SD*	*p-value*
Age *(years)*	36.27 ± 7.928	37.83 ± 8.276	0.529
Sex distribution *(female, n)*	18	21	0.440
BMI (Kg/m^2)	25.655 ± 2.874	26.402 ± 1.996	0.184
Marital status *(n, married)*	37	35	0.500
Educational status *(% educated)*			0.061
Bachelors	10	15	
Intermediate	8	15	
Professional	15	7	
Uneducated	8	4	
Religion (n Hindus)	36	37	0.500
Eating habits (n, Vegetarian)	36	32	0.240
Family type (n Joint)	13	15	0.641
Socio-economic Status			0.130
Lower class	8	11	
Middle class	33	27	
Upper class	0	3	

Although randomisation ensured balance in most sociodemographic variables, baseline differences were observed in key clinical outcomes (HAMD-17, YMRS, WHODAS 2.0, CRP). Between-group analyses were therefore adjusted for baseline values using ANCOVA, and the adjusted results were consistent with the primary findings.

Both the experimental and the control groups were significantly different at baseline in the scores of HAMD-17 (see Table 3). The proportion of the sample having fewer depressive symptoms at the end of the study was 70.7% in the experimental group and 48.8% in the control group. These results indicate that IPSRT with pharmacotherapy was superior to pharmacotherapy alone in reducing depressive symptoms.

Table 3. Effect on depression symptoms

Time Point	Control Group	Experimental Group	Between Group	Within-Group	
				Experimental Group	Control Group
	Mean ± SD	*Mean ± SD*	*p-value*	*p-value*	*p-value*
Baseline	17.68 ± 3.13	19.75 ± 3.01	0.040	—	—
Six weeks	17.02 ± 2.99	14.25 ± 2.05	0.001	<0.001	0.030
12 weeks	16.44 ± 2.80	12.00 ± 1.72	0.000	<0.001	0.012

Between-group p-values adjusted for baseline differences using ANCOVA.

At baseline, YMRS scores were significantly higher in the control group compared with the experimental group (see table 4). At the final measurement, the difference between the groups at 3 months was about eight points in favour of the experimental group. These findings show that IPSRT with pharmacotherapy was much more effective in the mitigation of manic symptoms compared to pharmacotherapy alone.

Table 4. Effect on manic symptoms

Time Point	Control Group	Experimental Group	Between Group	Within-Group	
				Experimental Group	Control Group
	Mean ± SD	*Mean ± SD*	*p-value*	*p-value*	*p-value*
Baseline	22.32 ± 4.88	18.24 ± 4.01	0.036	—	—
Six weeks	21.45 ± 4.12	15.12 ± 3.10	0.003	<0.001	0.019
12 weeks	20.22 ± 3.54	12.37 ± 2.27	0.000	<0.001	0.007

WHODAS 2.0 baseline scores were significantly higher in the experimental group compared with the control group (see Table 5). At 3 months, both the experimental and the control groups recorded a reduction. Significant within-group

improvements were also observed over time in each group. These results indicate that IPSRT with pharmacotherapy was associated with a higher rate of functional recovery compared to pharmacotherapy alone.

Table 5. Effect on disability scores

Time Point	Experimental Group *Mean ± SD*	Control Group *Mean ± SD*	Between Group *p-value*	Within-Group Experimental Group *p-value*	Within-Group Control Group *p-value*
Baseline	75.27 ± 3.02	78.56 ± 7.21	0.000	—	—
Six weeks	70.50 ± 4.50	71.10 ± 6.45	0.720	<0.001	<0.001
12 weeks	57.17 ± 6.28	55.11 ± 3.42	0.048	<0.001	<0.001

The baseline CRP levels were higher in the experimental group compared with the control group. The between-group difference was not significant at 6 weeks but became significant at 12 weeks. These findings indicate that the IPSRT plus pharmacotherapy combination proved more effective in reducing systemic inflammation than pharmacotherapy alone.

Table 6. Effect on systemic inflammation biomarker scores

Time Point	Experimental Group *Mean ± SD*	Control Group *Mean ± SD*	Between Group *p-value*	Within-Group Experimental Group *p-value*	Within-Group Control Group *p-value*
Baseline	9.99 ± 6.66	12.05 ± 3.46	0.000	—	—
Six weeks	8.85 ± 3.20	9.40 ± 2.88	0.188	<0.001	0.016
12 weeks	7.60 ± 3.33	8.26 ± 2.54	0.031	<0.001	0.009

The Figure 2 shows a snapshot of the IPSRT intervention on the outcomes listed above as a collection of line graphs.

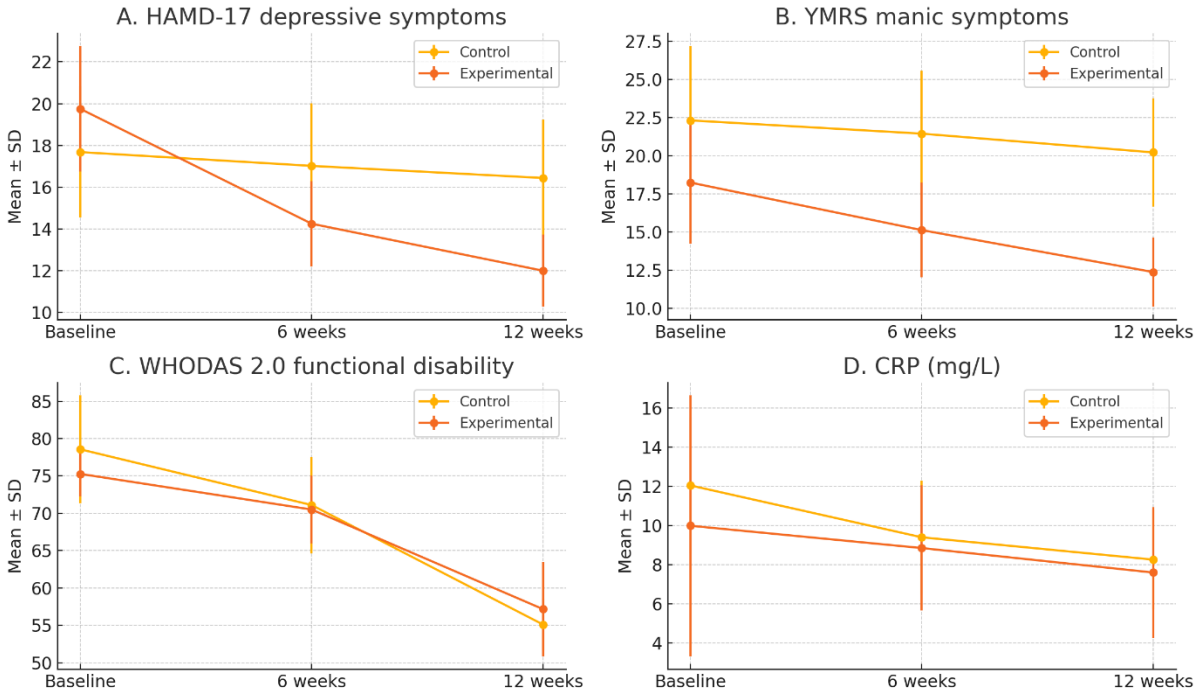

Figure 2. Effect of IPRST outcomes on BPAD patients.

Panels show mean (±SD) scores at baseline, 6 weeks, and 12 weeks for (A) HAMD-17 depressive symptoms; (B) YMRS manic symptoms; (C) WHODAS 2.0 functional disability; and (D) C-reactive protein (CRP, mg/L). Lines depict group means for the experimental (IPSRT + pharmacotherapy) and control (pharmacotherapy alone) groups; error bars represent standard deviations. Each arm had n = 41. IPSRT, Interpersonal and Social Rhythm Therapy; HAMD-17, 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0; CRP, C-reactive protein.

Subgroup analysis indicated that that there was no effect of age or gender (shown in Figure 3 and Figure 4).

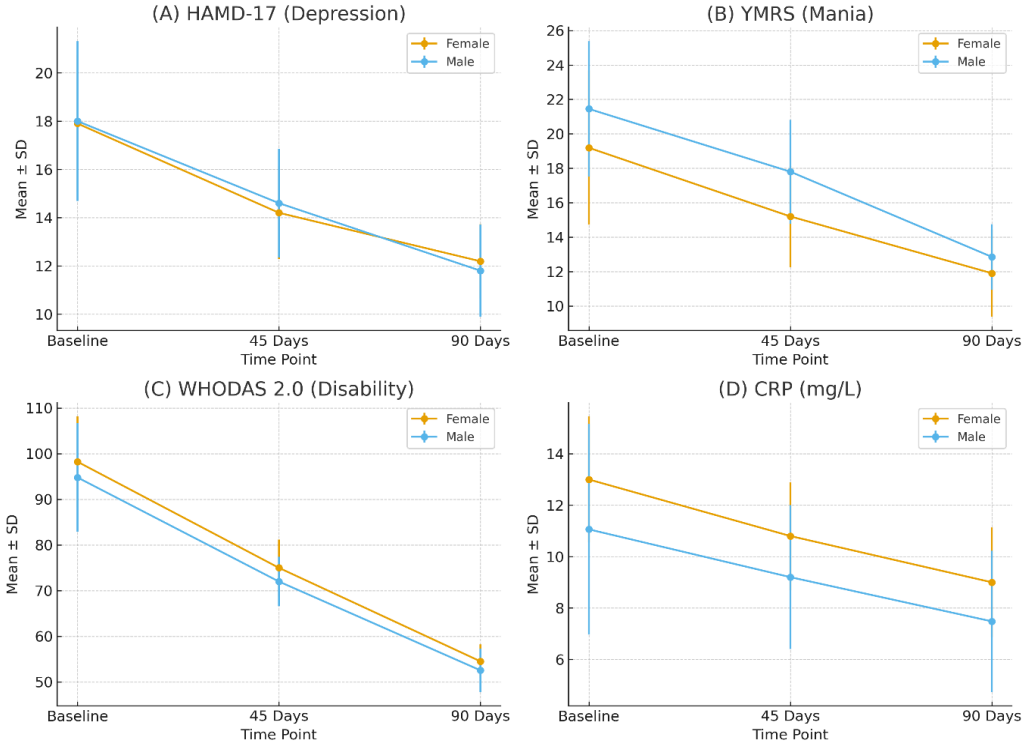

Figure 3. IPSRT outcomes by gender across time-points

Panels illustrate mean (±SD) scores at baseline, 45 days, and 90 days for female and male participants in the experimental group receiving Interpersonal and Social Rhythm Therapy (IPSRT) with pharmacotherapy. Outcomes measured include: (A) HAMD-17 depressive symptoms, (B) YMRS manic symptoms, (C) WHODAS 2.0 functional disability, and (D) C-reactive protein (CRP, mg/L). Each panel compares trends in male and female participants. IPSRT, Interpersonal and Social Rhythm Therapy; HAMD-17, 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0; CRP, C-reactive protein.

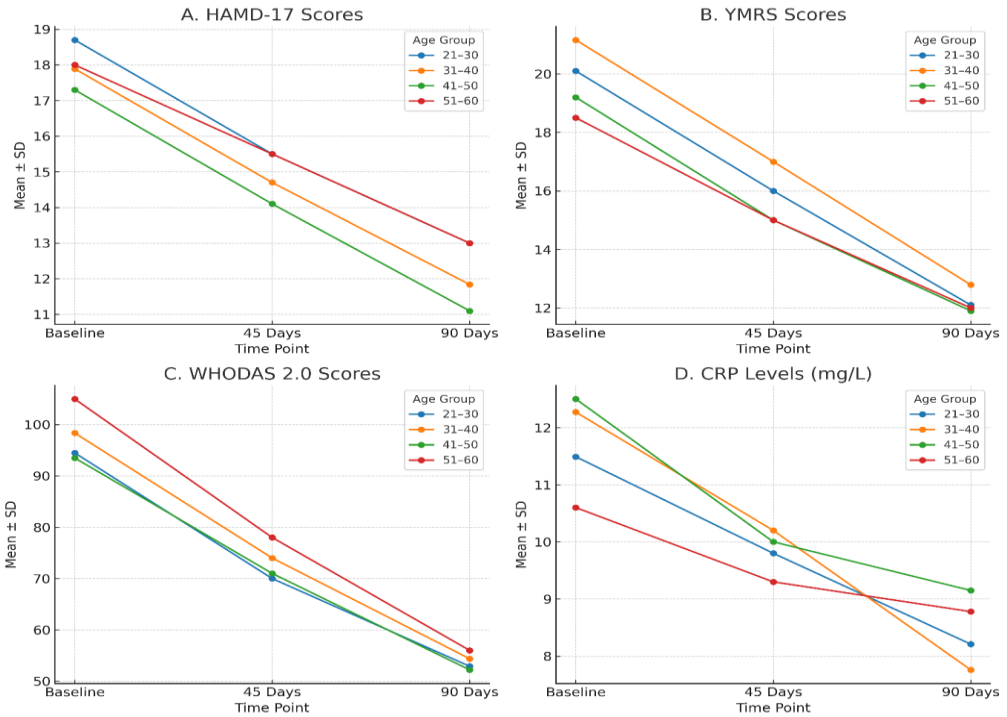

Figure 4. Effect of IPSRT on outcomes by age groups

Panels depict mean (±SD) scores at baseline, 45 days, and 90 days across age groups (21–30, 31–40, 41–50, 51–60 years) for (A) HAMD-17 depressive symptoms; (B) YMRS manic symptoms; (C) WHODAS 2.0 functional disability; and (D) C-reactive protein (CRP, mg/L). All participants received IPSRT in combination with pharmacotherapy. Scores improved across all age groups. Error bars represent standard deviations. IPSRT, Interpersonal and Social Rhythm Therapy; HAMD-17, 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0; CRP, C-reactive protein.

No severe adverse events were reported during the intervention period. Minor adverse events (e.g., headache, fatigue) were reported equally across groups and did not lead to discontinuation.

4. DISCUSSION

In the study, the authors sought to investigate the extent to which the combination of IPSRT to normal pharmacological treatment would result in better outcomes on patients with BPAD than pharmacotherapy alone. Results were consistent with the hypothesis: patients in the IPSRT plus medication group had more improvement in the depressive scores (HAMD-17) and manic scores (YMRS). In addition to having lower symptoms, the IPSRT group showed significant improvement in the functional ability as well lower WHODAS 2.0 scores. It is also important to note that systemic inflammation markers decreased significantly, with more pronounced changes in the CRP concentrations in the experimental arm. These findings imply that IPSRT, in combination with medication, may treat symptoms of mood improvement, functional performance, and systemic inflammation reduction of individuals with BPAD.

These improvements on depressive and manic symptoms, as well as statistically significant changes in disability, WHODAS 2.0 scores, and inflammatory burden, CRP levels align with and extend earlier findings. According to Nambiar and team (18), brief CBT showed significant improvements in residual affective symptoms and medication adherence but not functional. Conversely, the current study showed significant improvement in clinical and functional area. In a similar study, Kavitha et al. (17) noted the enhancement of the functioning of family-focused nursing interventions without a corresponding measurement of the severity of symptoms or biological indicators. It is interesting to note that our study differs with Carracedo-Sanchidrian and others (15) who did not find any incremental benefit of MBCT compared to psychoeducation on neurocognitive or neurotrophic outcomes. IPSRT had greater efficacy, implying it affected both core affective symptoms and everyday functioning, as compared to integrative or metacognitive protocols (13,16), which mainly focused on cognitive and social functioning. Notably, the current trial is the first to measure CRP as a biological outcome, and preliminary evidence is that psychotherapeutic interventions might have an ant inflammatory effect. This is, to our knowledge, one of the first Indian randomised controlled trials in BPAD to incorporate a biomarker outcome thereby facilitating the gap between the psychosocial and the biological schools of psychiatry. These findings support the clinical effectiveness of structured, rhythm-based psychosocial treatments as an effective add-on to pharmacotherapy in BPAD.

The participants between the ages of 31 and 50 years were more responsive to the intervention in terms of affective symptoms, functioning and CRP levels. This may reflect greater life stability, neuroplasticity, and motivation. They may also be linked to psychotherapy responsiveness by hormonal modulators, cortisol and oxytocin (26), which were not assessed directly in this study. There were no significant gender patterns although there might be some underlying hormonal or behavioural effects. According to the prior literature, the outcomes may be mediated by intra- and interpersonal dynamics, not by demographic factors alone (27). The results are in line with international RCTs (e.g., 12 and 13) and the demand of Serbetci (29) to obtain more mechanistic information about demographic moderators of psychotherapy response in BPAD.

The therapeutic effects of IPSRT are probably due to several overlapping mechanisms. Top on the list is the stabilisation of the circadian rhythms, which is the central dysfunction in BPAD. IPSRT also helps to synchronise the biological rhythms with environmental cues through reinforcement of regular sleep-wake cycles, meal timing and daily routines to minimise affective lability. Previous models of pathophysiology of BPAD are highly supportive of this chronotherapeutic effect. The component of interpersonal skills has the role of regulating emotions and improving social functioning. These are interpersonal benefits as explained by Serbetci (29), which are the main active ingredients to achieve long-term mood enhancement. Also, psychoeducation in IPSRT promotes compliance and makes patients have a better knowledge of their condition which are the robust determinants of clinical stability.

Notably, the significant decrease in CRP can be suggestive of a decrease in the systemic inflammatory processes which might be a manifestation of decreased psychosocial stress and allostatic load. This attests to neurobiological theories of the relationship of psychotherapy on immunomodulation, specifically through HPA axis dampening (26). Finally, contextual therapeutic factors in IPSRT, namely alliance, structure and patient agency (28) could enhance the benefit of this treatment, thus suggesting the need to have a holistic and person-focused psychosocial intervention in BPAD.

This paper demonstrates the importance of using IPSRT as part of the standard practice in managing BPAD. IPSRT in combination with pharmacotherapy reduced symptoms of mood disorder, improved functioning, and decreased inflammation, as shown by low levels of CRP, and thus, taking into consideration both psychological and physiological elements of the disease. IPSRT needs to be time-limited and structured and affordable, which makes it applicable to the setting with fewer resources. Its emphasis on controlling circadian rhythm, interpersonal skills, and compliance can be used to prevent the relapse and foster recovery. Such psychosocial treatments should be early in clinical pathways to improve the long-term outcomes in BPAD.

Internal validity of this study is also reinforced by the strong randomised controlled design. The use of validated scales (HAMD-17, YMRS, WHODAS 2.0) was used to provide reliable mood and functional outcome measurement. Inclusion of a biomarker, CRP, gave an objective value to which clinical response could be attributed to an underlying inflammation. It was administered by trained psychiatric professionals in normal clinical practice, which increases its applicability to a real-life scenario. This multidimensional design of the study, which measures symptom reduction, functional recovery, and biological change, provides a rich analysis of the clinical utility of IPSRT in the treatment of BPAD.

Despite its strengths, the study has several limitations. There are the drawbacks of the small sample size and a fairly small follow-up period of three months. The follow-up was three months which is not sufficient to determine the long-term sustainability of the clinical gains especially in terms of relapse prevention and maintaining functions. The intervention could not be blinded as to the group assignment of therapists, thus providing the risk of expectancy or performance bias. Also, the study failed to include the structured assessments of the relapse episodes or a fine-grained examination of medication adherence that are relevant in assessing overall treatment outcomes. Another limitation of the study is that, despite randomisation, baseline imbalances were observed in some clinical variables (HAMD-17, YMRS, WHODAS 2.0, CRP). Although we performed adjusted analyses using ANCOVA to account for these differences, residual confounding cannot be entirely excluded. Lastly, since the study was done in one tertiary-care centre, the generalisability to other places especially in community or primary care might not be achieved.

Future research should incorporate longer follow-up periods to have a clearer idea on the long-term effects of IPSRT in the prevention of relapse and functional stability. The findings would be made more generalisable and subgroup analyses would be possible by increasing the number and variety of people involved in multi-centre trials. Additional research into the biological processes underlying the therapeutic effects of IPSRT including circadian gene expression, cortisol levels, or other neuroendocrine markers may help provide further insight into the mechanism of IPSRT. Head-to-head comparative trials could compare IPSRT and other evidence-based psychosocial interventions like CBT and FFT, which would assist in defining the relative efficacy and applicability of various methods. Also, the cost-efficiency and scalability of IPSRT should be explored especially in resource-constrained and practical clinical practice environments to provide evidence that can be used to make policy-level choices and integrate into general psychiatric practice.

5. CONCLUSION

This paper shows strong evidence that IPSRT yields much more improvement in depressive and manic symptoms, functional outcomes, and inflammatory markers than pharmacotherapy in patients with BPAD when added to standard pharmacotherapy. The multidimensional benefits were also played out by the structured and manualised nature of IPSRT that was designed to address circadian regulation, interpersonal functioning, and treatment adherence. These results highlight the paramount importance of the inclusion of psychosocial interventions into the traditional model of treatment of BPAD. IPSRT is a practical and successful complement to pharmacological treatment that favours a more comprehensive and patient-centred treatment.

Declarations

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Conflict of Interest Declaration

The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

Author Contributions

All authors contributed substantially to the conception and design of the study, data collection, analysis, and interpretation. Dr Satyajyoti Tiwari drafted the manuscript, and all authors critically revised it for intellectual content. All authors approved the final version and agree to be accountable for all aspects of the work.

Data Availability Statement

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request, subject to institutional and ethical guidelines.

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