Two-Year Outcomes for Interpersonal and Social Rhythm Therapy in Individuals With Bipolar I Disorder

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**Context:** Numerous studies have pointed to the failure of prophylaxis with pharmacotherapy alone in the treatment of bipolar I disorder. Recent investigations have demonstrated benefits from the addition of psychoeducation or psychotherapy to pharmacotherapy in this population.

**Objective:** To compare 2 psychosocial interventions: interpersonal and social rhythm therapy (IPSRT) and an intensive clinical management (ICM) approach in the treatment of bipolar I disorder.

**Design:** Randomized controlled trial involving 4 treatment strategies: acute and maintenance IPSRT (IPSRT/IPSRT), acute and maintenance ICM (ICM/ICM), acute IPSRT followed by maintenance ICM (IPSRT/ICM), or acute ICM followed by maintenance IPSRT (ICM/IPSRT). The preventive maintenance phase lasted 2 years.

**Setting:** Research clinic in a university medical center.

**Participants:** One hundred seventy-five acutely ill individuals with bipolar I disorder recruited from inpatient and outpatient settings, clinical referral, public presentations about bipolar disorder, and other public information activities.

**Interventions:** Interpersonal and social rhythm therapy, an adaptation of Klerman and Weissman’s interpersonal psychotherapy to which a social rhythm regulation component has been added, and ICM.

**Main Outcome Measures:** Time to stabilization in the acute phase and time to recurrence in the maintenance phase.

**Results:** We observed no difference between the treatment strategies in time to stabilization. After controlling for covariates of survival time, we found that participants assigned to IPSRT in the acute treatment phase survived longer without a new affective episode (P = .01), irrespective of maintenance treatment assignment. Participants in the IPSRT group had higher regularity of social rhythms at the end of acute treatment (P < .001). Ability to increase regularity of social rhythms during acute treatment was associated with reduced likelihood of recurrence during the maintenance phase (P = .05).

**Conclusion:** Interpersonal and social rhythm therapy appears to add to the clinical armamentarium for the management of bipolar I disorder, particularly with respect to prophylaxis of new episodes.

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Several groups have adapted the cognitive therapy of Beck et al for treatment of bipolar disorder. Lam et al found a reduction in rate of relapse, improved medication adherence, improved psychosocial functioning, fewer days in a bipolar episode, and fewer hospital admissions in the cognitive therapy group. A recent follow-up report showed continued benefits 2 years after treatment. In a pilot study of 42 patients with bipolar I or II disorder, Scott et al demonstrated that another adaptation of cognitive therapy resulted in greater improvements in symptoms and functioning at the 6-month follow-up. Results of a subsequent large, multicenter trial are yet to be reported.

Miklowitz and Goldstein developed a 9-month family-focused psychoeducational treatment. Results from an initial pilot study and 2 subsequent randomized trials have all indicated positive effects for this intervention. In the first of the larger trials reported, family-focused treatment significantly increased survival time without a new mood episode over a 2-year period. Rea et al subsequently reported that, among individuals recently hospitalized for mania, those assigned to family-focused treatment were less likely to be rehospitalized during treatment and experienced fewer relapses over the 2 years of the study.

We report on a randomized trial of interpersonal and social rhythm therapy (IPSRT) as both an acute- and maintenance-phase treatment. Interpersonal and social rhythm therapy is an adaptation of interpersonal psychotherapy, based on our social zeitgeber hypothesis, which posits that unstable or disrupted daily routines lead to circadian rhythm instability and, in vulnerable individuals, to affective episodes. Subsequent studies of rhythm-disrupting life events suggested that such events were indeed implicated in the onset of bipolar episodes. We hypothesized that IPSRT would be associated with shorter time to remission and longer time to recurrence during a 2-year maintenance phase than an intensive clinical management (ICM) approach.

**METHODS**

The Maintenance Therapies in Bipolar Disorder study, conducted between 1991 and 2002, compared 2 psychosocial interventions for patients with bipolar I disorder: IPSRT and ICM, an adaptation of the clinical management strategy used in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. Acutely ill patients were randomly assigned to 1 of 4 treatment strategies: acute and maintenance IPSRT (IPSRT/IPSRT), acute and maintenance ICM (ICM/ICM), acute IPSRT followed by maintenance ICM (IPSRT/ICM), or acute ICM followed by maintenance IPSRT (ICM/IPSRT) (Figure 1). All study participants received protocol-driven pharmacotherapy. Participants who experienced a new affective episode during the preventive maintenance phase remained in their randomly assigned psychosocial treatment and were treated pharmacologically according to the polarity of the new episode.

**PARTICIPANTS**

Study participants were 175 individuals between 18 and 60 years of age with a lifetime diagnosis of bipolar 1 disorder or schizoaffective disorder, manic type, according to Research Diagnostic Criteria in their third or greater lifetime affective episode. The index episode was required to meet minimum severity criteria: a score of 13 or greater on the 17-item Hamilton Depression Rating Scale (HDRS) if depressed or a score of 15 or greater on the Bech-Rafaelsen Mania Scale (BRMS), if manic or mixed. Exclusion criteria included current rapid cycling (≥4 episodes per year), chronic drug or alcohol abuse, pregnancy or uncontrolled medical illness that would preclude protocol pharmacotherapy, meeting full criteria for borderline or antisocial personality, and active bulimia or anorexia. No other Axis I or II disorder constituted an exclusion.

**MEASURES**

Initially, diagnostic determinations were made using the Schedule for Affective Disorders and Schizophrenia. After 1995, we used the Structured Clinical Interview for DSM-IV-Patient Version for this purpose; however, presence of an affective episode was confirmed at study entry and at point of recurrence using the Research Diagnostic Criteria for all study subjects. We used the 17-item and 25-item versions of the HDRS and Bech-Rafaelsen Mania Scale (BRMS) to determine severity of depression and mania. On-going assessments were conducted by nonblind, independent clinical evaluators at each study visit. Evaluators were trained to a criterion level of agreement (intraclass correlation coefficient ≥0.80), which was recalibrated every 6 months. Recurrence was determined by blind senior psychiatrists who were not otherwise involved in the conduct of the study and who were asked to determine whether the participant met Research Diagnostic Criteria for a new affective episode. This procedure was bypassed when the participant required immediate hospitalization.
Severity of medical illness was assessed using the Duke Severity of Illness Checklist. Meeting the World Health Organization (Geneva, Switzerland) and International Obesity Task Force (London, United Kingdom) criteria for obesity (body mass index ≥30) at baseline was included as a medical comorbidity in all analyses.

Subjects who were assigned to ICM completed the Social Rhythm Metric I (SRM I), a measure of the regularity of daily routines, while IPSRT subjects completed the SRM II, an adaptation of SRM I designed to aid participants in increasing the regularity of daily routines. On both versions, participants recorded the time at which 17 activities (eg, getting out of bed, having breakfast, beginning work, engaging in a hobby) occurred each day. Data from a given week are scored as a unit, yielding an overall score between 0 and 7 (higher=more regular). Earlier investigations had found the mean SRM score to be 3.4±0.82 among men and women aged 20 to 40 years in the general population.

To evaluate the specificity of the IPSRT and ICM conditions, trained raters used an adaptation of the Therapy Rating Scale. This 22-item scale evaluates the extent to which sessions focused on intervention-specific themes and yields an interpersonal, social rhythm, and somatic subscale score for each session. Raters maintained a criterion level of agreement within 1 point (intraclass correlation coefficient ≥0.80 for each scale item). Analyses of Therapy Rating Scale data indicated that IPSRT sessions differed significantly from ICM sessions on all 3 subscales during the acute phase (interpersonal, z=6.3, P<.001; social rhythm, z=2.0, P=.04; somatic, z=−6.1, P<.001) and on the interpersonal (z=5.3, P<.001) and somatic (z=−5.8, P<.001) subscales during the maintenance phase of the trial. Serum drug levels of lithium and other mood stabilizers were evaluated at each clinic visit using standard laboratory methods.

PROCEDURE

Study participants were recruited from the inpatient units and outpatient clinics of Western Psychiatric Institute and Clinic (Pittsburgh, Pa), from area clinicians, and through public presentations and other public information activities on the topic of bipolar disorder. The University of Pittsburgh (Pittsburgh) biomedical institutional review board approved all recruitment, assessment, and treatment procedures. Individuals who met all inclusion and exclusion criteria provided written informed consent after receiving a complete description of the study and having an opportunity to ask questions.

Participants were seen weekly until stabilization was achieved (4 consecutive weeks during which both HDRS scores from the 17-item version and BRM5 scores averaged ≤7). Visits in the preventive phase were scheduled every other week for 12 weeks and then monthly until the end of the 2-year maintenance phase. The ICM/IPSRT group was seen for weekly visits for the first 12 weeks of the preventive phase to facilitate the introduction of IPSRT. Study participants were treated by teams consisting of a nonphysician clinician (social worker, nurse, or psychologist) and a psychiatrist. Nonphysician clinicians provided both IPSRT and ICM. Subjects’ treatment teams remained the same throughout the protocol.

TREATMENT

Interpersonal and social rhythm therapy is described in detail in an earlier report and in the treatment manual. Briefly, IPSRT is based on our social zeitgeber hypothesis and the conviction that regularity of social routines and stability of interpersonal relationships have a protective effect in recurrent mood disorders. The treatment focuses on the links between mood symptoms and quality of social relationships and social roles, the importance of maintaining regularity in daily routines, and the identification and management of potential precipitants of rhythm disruption. The interpersonal aspects of IPSRT derive largely from interpersonal psychotherapy and maintenance interpersonal psychotherapy and thus focus on resolution of current interpersonal problems (unresolved grief, interpersonal disputes, role transitions, and interpersonal deficits) and prevention of future problems in these areas. An additional problem area specific to bipolar I disorder, termed “grief for the lost healthy self,” is addressed to facilitate mourning the life the patient might have had were it not for the illness and the limitations it sets. Sessions of IPSRT generally lasted 45 to 55 minutes.

Therapists providing IPSRT had previously been trained in interpersonal therapy. They then completed 2 IPSRT training cases under our individual supervision (E.F.) or that of Debra Frankel, ACSW, or Steve Carter, PhD, codevelopers of the treatment. All therapists participated in ongoing group supervision that we (E.F.) led on a biweekly basis throughout the course of the study.

Intensive clinical management is a manual-driven approach to the medical management of bipolar disorder that we developed based on the clinical management strategies employed in the National Institute of Mental Health Treatment of Depression Collaborative Research and in our own earlier study of Maintenance Therapies in Recurrent Depression. The specific elements of ICM include (1) education about bipolar disorder, (2) education about the medications used to treat bipolar disorder, (3) education about basic sleep hygiene, (4) careful review of symptoms, (5) careful review of adverse effects, (6) medical and behavioral management of adverse effects, and (7) nonspecific support. Sessions of ICM generally lasted 20 to 25 minutes.

Although the Maintenance Therapies in Bipolar Disorder study was an outpatient protocol, severely ill participants began their pharmacotherapy on an inpatient basis. Acute pharmacotherapy was provided by study physicians who employed specific treatment algorithms for depressive, manic, and mixed episodes. The goal of the pharmacotherapy was to stabilize the maximum number of participants possible on lithium monotherapy or lithium and a single other agent. Participants with a past history of lithium intolerance and those who refused to take lithium were prescribed sodium divalproex or carbamazepine. Generally, individuals in an acute manic episode were rapidly titrated to a lithium serum level of 0.8 to 1.0 mEq/L, with higher levels permitted if response was not achieved. When lithium alone failed to bring about a response, an antipsychotic medication was added. Originally, perphenazine, in a dosage range of 8 to 24 mg, was used for this purpose in the earlier years of the study. Later, atypical antipsychotic medications were used. Participants presenting in a mixed episode were generally treated in a similar fashion.

Individuals presenting in a depressive episode were also begun on lithium. Antidepressant medication was added when lithium alone failed to bring about a response. Our treatment algorithm called initially for the use of tranylcypromine sulfate as an adjunctive antidepressant. For second-line antidepressants, we initially employed imipramine hydrochloride and later selective serotonin reuptake inhibitors. A small number of participants were prescribed other medications when these strategies did not lead to stabilization. The target serum level of lithium for the end of acute treatment was 0.8 to 1.0 mEq/L. Lower levels (minimum, 0.5 mEq/L) were permitted if participants could not tolerate a level of 0.8 mEq/L without severe adverse effects.
Once participants entered the maintenance phase, no changes were permitted in their medication regimens with 2 exceptions. Lithium dosages could be adjusted to maintain the target serum level. When patients called to report sudden severe insomnia or other indicators of an acute onset of mania, the protocol permitted the use of 3 to 5 days of rescue medication, consisting of perphenazine (2-16 mg/d) or thioridazine hydrochloride (25-200 mg/d). If symptoms did not resolve within 5 days, the medication was stopped and the participant was evaluated for recurrence.

**RANDOMIZATION PROCEDURES**

The randomization sequence was generated by simple randomization. No blocking or stratification was employed. Once a patient consented to participation, the study coordinator phoned the individual responsible for the randomization, obtained the participant’s acute treatment assignment, and informed the participant’s clinicians. All program staff and study participants remained blind to the maintenance treatment assignment until the participant met stabilization criteria. At that time, the study coordinator again called the individual responsible for the randomization to obtain the participant’s maintenance treatment assignment and then informed the treatment team.

As no long-term study of psychosocial treatment of bipolar I disorder had been published when this study was designed, we based our sample size and power estimations on the pharmacotherapy plus clinical management outcomes in the bipolar disorder arm of the National Institute of Mental Health Collaborative Study Group investigation and on effect sizes obtained in studies of psychosocial treatment of schizophrenia. We assumed a conservative attrition rate of 40% in the obtained in studies of psychosocial treatment of schizophrenia. We also compared medication adherence, defined as coefficient of variation of mood stabilizer medication, using analysis of variance. Treatment specificity was assessed by comparing Therapy Rating Scale subscale scores using the Wilcoxon rank sum test. Treatment outcome was assessed using Cox proportional hazards survival models. We explored the impact of change in social rhythm stability on treatment outcome using functional principal components analysis. One of us (W.T.) conducted the functional principal components analysis using R version 1.9.0. All other analyses were performed using R or version 8 of SAS for Windows. All tests were considered significant at α = .05 (2-tailed).

**RESULTS**

Demographic and clinical characteristics of the study participants are displayed in Table 1. Median time to stabilization was 18.7 weeks (95% confidence interval, 14.7-25.1). Survival analysis, covarying for age, sex, marital status, index episode polarity, medical burden, history of anxiety disorder, history of alcohol or substance abuse, and baseline HDRS and BRMS scores, indicated no significant difference between IPSRT and ICM in time to remission, nor was there a difference in the proportion achieving remission (IPSRT, 70%; ICM, 72%). We observed 54 recurrences (27 depressive, 17 manic, and 10 mixed) among the 125 participants during the 2-year maintenance treatment phase, or an overall recurrence rate of 43.2%. Raw 2-year recurrence rates for the 4 treatment strategies were 41% for IPSRT/IPSRT, 41% for IPSRT/ICM, 28% for ICM/ICM, and 63% for ICM/IPSRT.

To examine the effect of the 4 treatment strategies on time to recurrence in the maintenance phase, we fit a survival model using the same group of covariates. Treatment assignments in the acute and maintenance phase treatments were separately compared using contrasts. The first contrast, acute ICM vs acute IPSRT, produced an es-
timate of 1.75 (P = .04), indicating a significant increase in hazard ratio for those patients randomized into ICM during the acute phase. The second contrast, maintenance ICM vs maintenance IPSRT, produced an estimate of 0.19 (P = .88). Because maintenance-treatment assignment had no significant effect on time to recurrence, all further models considered only randomization in the acute phase.

Subsequent survival analysis employing the same covariates comparing the effect of the 2 acute treatment arms on time to recurrence in the maintenance phase using a backward stepwise selection procedure indicated that participants assigned to IPSRT in the acute phase survived significantly longer without a new mood episode (z = -2.58, P = .01, hazard ratio, 0.34). Married participants (z = -3.58, P < .001, hazard ratio, 0.25) also experienced longer survival, and those who entered the study in a mixed episode recurred more quickly (z = 2.62, P = .009, hazard ratio, 1.39). A similar pattern was observed for lifetime anxiety disorders (z = 2.76, P = .006, hazard ratio, 5.61; Table 2). After we controlled for marital status, index episode polarity, history of anxiety disorder, and medical burden, the effect size of acute-phase IPSRT for patients with the mean number of inactive medical comorbidities (1.76) was a hazard ratio of 0.58. Analysis of variance comparing coefficient of variation of mood-stabilizer serum levels indicated no significant difference among the 4 treatment strategies in terms of medication adherence (F1,117 = 1.3, P = .29).

We found no difference among the treatment conditions in average level of affective symptoms (25-item HDRS score plus BRMS score) over the course of the maintenance phase (F3,112 = 1.3, P = .29). After controlling for marital status, medical comorbidity, and anxiety history, there still was no difference among the treatment conditions (F3,117 = 0.46, P = .74); however, number of active medical comorbidities was related to total symptom scores (F1,117 = 7.49, P = .007) as was lifetime history of anxiety disorder (F1,117 = 5.16, P = .03).

To compare the effect of IPSRT and ICM on SRM scores during the acute phase, a linear mixed-effects model was fit with SRM score as the response and time in acute phase (weeks) as the covariate. The likelihood equations for this model were modified to account for the possible effect of variation in remission times on longitudinal SRM scores. The treatments differed significantly on SRM scores (intercept, 3.72 for IPSRT vs 3.23 for ICM, P < .001; slope, 0.015 for IPSRT vs 0.01 for ICM, P = .06).

To explore the extent to which the protective effect of IPSRT might be related to increases in the regularity of so-
We conducted a 2-phase trial comparing 2 manual-based psychosocial treatment approaches, IPSRT and ICM, in the acute and maintenance treatment of individuals with bipolar I disorder. The design of the study, in which the same clinicians treated subjects in both treatment conditions and for a comparable number of sessions, provided a stringent test of differences between the treatments.

After controlling for variables that had significant effects on long-term outcome, we found that participants who received IPSRT in the acute treatment phase experienced longer survival time without a new affective episode and were more likely to remain well for the full 2 years of the preventive maintenance phase. This effect appeared to be mediated by the substantially increased regularity of social routines among subjects receiving IPSRT.

One interpretation of the finding of the better outcomes for participants receiving acute IPSRT is that it simply reflects the increased attention provided in IPSRT sessions, which were generally 20 to 25 minutes longer than ICM sessions. However, because the benefit of IPSRT appears to be mediated by increased social rhythm stability, a specific effect of IPSRT, this seems unlikely. Furthermore, IPSRT was not beneficial to all participants assigned to this condition. As discussed later, those with higher levels of medical burden actually fared better when assigned to the more somatically focused ICM condition.

The study outcome is consistent with our social zeitgeber hypothesis concerning the relationship between social rhythm stability and risk of new episodes in individuals with recurrent mood disorders. It is interesting that increasing social rhythm stability during acute treatment was associated with reduced risk of recurrence regardless of the treatment received in the maintenance phase. This observation begins to address the question of when IPSRT should be initiated: when an individual is still in an acute episode of illness or during a period of stability. The present study suggests that it is immediately following an acute episode that individuals are most motivated to make the sometimes demanding changes in lifestyle that are required to achieve stable social rhythms.

The fact that we found no difference between the 2 psychosocial treatments in terms of time to remission may be related to the heterogeneity of the index episodes treated in this trial. To date, there is no evidence that psy-
Chootherapy facilitates recovery from mixed or pure manic states. However, even among subjects presenting in a depressive episode, the additive effect of IPSRT did not approach significance. With only 50 depressed subjects per arm, power to detect such a difference may not have been adequate. Alternatively, this finding may be understood with reference to the literature on the treatment of acute episodes of unipolar depression. Specifically, of the several more contemporary studies that have examined the possible benefit of combined pharmacotherapy and psychotherapy vs pharmacotherapy alone in the treatment of depressive disorders, about half have found significant additive effects and half have not.

The fact that individuals with bipolar disorder are at increased risk for a variety of serious medical illnesses, particularly cardiovascular disease, diabetes, and pulmonary problems, has been well documented in the literature, but few if any studies have examined the impact of medical illness on acute or long-term treatment outcome. We found that serious medical illness had a negative effect on time to remission, on well time following remission, and on levels of interepisode subsyndromal symptoms.

We also found interesting statistical interactions between medical illness and anxiety and the relative benefits of IPSRT and ICM. Participants in good physical health who received IPSRT in the acute phase had good long-term outcomes. In contrast, those with medical problems or anxiety disorders actually fared better if they were assigned to ICM in the acute phase. Initially, we found this result puzzling; however, when we considered the content of each of these modalities, it makes sense. In IPSRT, the therapist is to concentrate on increasing social rhythm stability and improving the patient’s interpersonal relationships while specifically avoiding a focus on somatic complaints. In ICM, the therapist is enjoined to focus on the patient’s somatic complaints. This may have had a series of benefits for study participants with multiple medical illnesses, including better medical management of their illnesses by study physicians, more help in problem-solving as to how they could cope with medical illness, and a greater sense of being understood and supported by their clinicians. In contrast, medically burdened and anxious study participants assigned to IPSRT may have found it difficult to put aside their somatic focus and turn their attention to the work of IPSRT.
Participans who were married at baseline had significantly better long-term outcomes than those who were not. In this case, marital status could be acting as a proxy for a variety of variables, including a somewhat later onset of illness (allowing the individual to achieve more developmental milestones, maturity, and a broader support network before being challenged by bipolar disorder); a social routine that is at least partially stabilized by another individual; and greater social support that may attenuate the negative effects of stressful life events on mood.

Our results suggest that the patient who is most likely to benefit from IPSRT as it is currently conceptualized is the medically healthier individual without a history of anxiety disorder. Indeed, in an earlier report on a subset of the individuals included in this report, we demonstrated that those with higher levels of lifetime panic spectrum symptoms showed longer times to remission of the acute bipolar episode. Our present findings suggest that for such patients, IPSRT would benefit from the same kinds of modifications we are currently making to interpersonal therapy to meet the needs of unipolar patients whose clinical picture is complicated by panic spectrum symptoms.

The Maintenance Therapies in Bipolar Disorder trial represents one of the larger studies conducted to date on psychosocial treatments for bipolar disorder. Levels of participant retention generally exceeded those observed in other long-term trials. Yet, despite its size and level of retention, the trial remained vulnerable to the vagaries of randomization. Variables that later proved to be strongly related to outcome, such as marital status and medical burden, were not distributed equally among the maintenance study conditions, making initial interpretation of the outcomes more complicated. Future studies of IPSRT, and perhaps other psychosocial treatments for bipolar disorder, might benefit from stratification on some of these variables. It will also be important to develop a measure that could test for mediation of outcome by changes in the interpersonal as well as social rhythm realms. Such a measure could facilitate a clearer understanding of the full range of active ingredients of this treatment.

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