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

Ellen Frank, PhD; David J. Kupfer, MD; Michael E. Thase, MD; Alan G. Mallinger, MD; Holly A. Swartz, MD; Andrea M. Fagiolini, MD; Victoria Grochocinski, PhD; Patricia Houck, MSH; John Scott, AM; Wesley Thompson, PhD; Timothy Monk, PhD

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.

Arch Gen Psychiatry. 2005;62:996-1004

Author Affiliations: Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

I N 1989, MORE THAN 40 YEARS AFter the discovery of lithium carbonate, bipolar disorder remained a major therapeutic challenge. Numerous studies[1-6] pointed to the frequent failure of prophylaxis with pharmacotherapy alone. That year, the National Institute of Mental Health (Bethesda, Md) Workshop on the Treatment of Bipolar Disorder[7] urged that research be directed to alternative drug strategies and to development of psychosocial interventions specific to bipolar disorder. At least 6 such interventions have now been studied in randomized controlled trials of adequate size and duration. All suggest that adding focused psychotherapy to pharmacologic management of bipolar disorder conveys benefit.

Perry et al[8] found that a brief (7- to 12-session) individual psychoeducational intervention emphasizing identification of prodromal signs reduced manic recurrences but had no effect on depressive recurrences over an 18-month period. Colom et al[9] demonstrated that a group psychoeducational intervention consisting of 20 ninety-minute sessions focused on the illness and its management was associated with longer survival time without a new episode of illness. Simon et al[10,11] conducted an effectiveness study of Bauer and McBride's[12] Life Goals Program of group therapy in the context of a broader

care management program in a large health maintenance organization. Care management participants reported fewer symptoms of mania through 12 months of follow-up.

Several groups have adapted the cognitive therapy of Beck et al[13] for treatment of bipolar disorder. Lam et al[14,15] 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[16] showed continued benefits 2 years after treatment. In a pilot study of 42 patients with bipolar I or II disorder, Scott el al[17] 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[18] developed a 9-month family-focused psychoeducational treatment. Results from an initial pilot study[19] and 2 subsequent randomized trials[20,21] have all indicated positive effects for this intervention. In the first of the larger trials reported,[20] family-focused treatment significantly increased survival time without a new mood episode over a 2-year period. Rea et al[21] 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)[22] as both an acute- and maintenance-phase treatment. Interpersonal and social rhythm therapy is an adaptation of interpersonal psychotherapy[23,24] based on our social zeitgeber hypothesis,[25,26] 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.[27,28] 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.[29] 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.
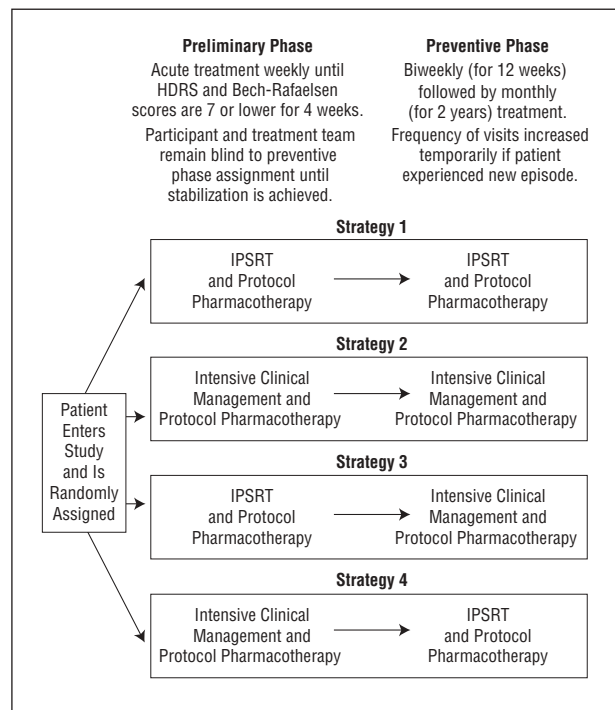

Figure 1. Maintenance therapies in bipolar disorder study design. IPSRT indicates interpersonal and social rhythm therapy; HDRS, Hamilton Depression Rating Scale.

PARTICIPANTS

Study participants were 175 individuals between 18 and 60 years of age with a lifetime diagnosis of bipolar I disorder or schizoaffective disorder, manic type, according to Research Diagnostic Criteria[30] in their third or greater lifetime affective episode. The index episode was required to meet minimum severity criteria: a score of 15 or greater on the 17-item Hamilton Depression Rating Scale (HDRS)[31] if depressed or a score of 15 or greater on the Bech-Rafaelsen Mania Scale (BRMS),[32] if manic or mixed. Exclusion criteria included current rapid cycling ($\geq$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.[33] After 1995, we used the Structured Clinical Interview for *DSM-IV*–Patient Version[34] 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[31,35] and the BRMS[32] to determine severity of depression and mania. Ongoing assessments were conducted by nonblind, independent clinical evaluators at each study visit. Evaluators were trained to a criterion level of agreement (intraclass correlation coefficient $\geq$ 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.[36] 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),[37] a measure of the regularity of daily routines, while IPSRT subjects completed the SRM II,[38] 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[39] had found the mean SRM score to be 3.43 ± 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.[40,41] 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 BRMS 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[22] and in the treatment manual.[42] Briefly, IPSRT is based on our social zeitgeber hypothesis[23,24] 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[24,25] and maintenance interpersonal psychotherapy[43] 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[44] employed in the National Institute of Mental Health Treatment of Depression Collaborative Research[29] and in our own earlier study of Maintenance Therapies in Recurrent Depression.[45] 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.
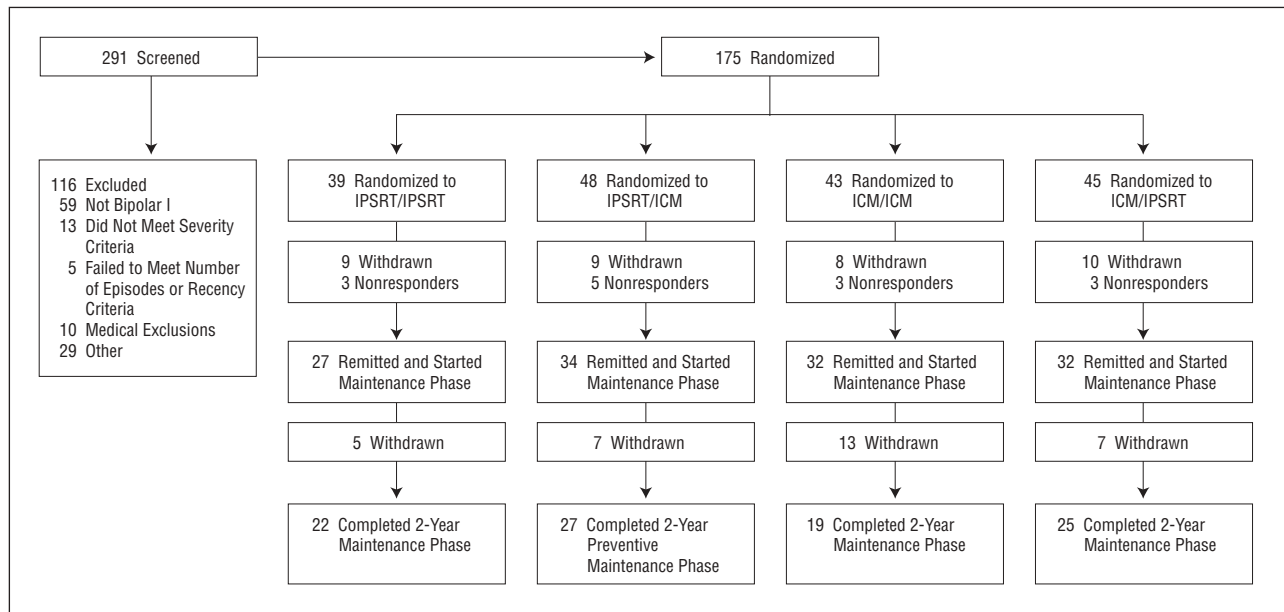
Figure 2. Flow chart of subject progress. ICM indicates intensive clinical management; IPSRT, interpersonal and social rhythm therapy.

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[46] and on effect sizes obtained in studies of psychosocial treatment of schizophrenia.[47-51] We assumed a conservative attrition rate of 40% in the acute treatment phase. On that basis, and with a goal of 80% power, we projected that we would need to enter 200 participants to have 30 to 36 patients per group enter the maintenance phase. Because our retention rate through the end of stabilization was greater than 70%, we ended recruitment at 175 study participants (**Figure 2**).

DATA ANALYSIS

Demographic and clinical characteristics of the study participants were compared using χ^2 tests for categorical variables, analysis of variance for approximately normally distributed continuous variables, and Kruskal-Wallis tests for nonnormally distributed continuous variables. 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.[52] All other analyses were performed using R or version 8 of SAS for Windows.[53] All tests were considered significant at $\alpha = .05$ (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-

Table 1. Baseline Demographic and Clinical Characteristics of 175 Study Participants

Variable	ICM/ICM (n = 43) Mean ± SD	Median	ICM/IPSRT (n = 45) Mean ± SD	Median	IPSRT/ICM (n = 48) Mean ± SD	Median	IPSRT/IPSRT (n = 39) Mean ± SD	Median	Test Statistic	df	P Value
Age, y	34.9 ± 10.8	34	35.0 ± 11.0	35	34.6 ± 10.1	36	36.4 ± 10.6	37	F = 0.3	3,171	.86
Women, %	51		53		56		67		χ² = 2.3	3	.51
White, %	86		96		90		90		χ² = 2.3	3	.50
Married, %	40		27		35		44		χ² = 2.9	3	.41
Education, y	14.7 ± 1.8	14	14.8 ± 1.8	14	14.6 ± 2.1	14	15.2 ± 2.0	1.4	χ² = 1.8	3	.61
Active medical comorbidities, No.	2.1 ± 1.9	2	1.8 ± 1.7	1	2.8 ± 2.5	2	3.1 ± 2.3	3	χ² = 10.1	3	.02
Inactive medical comorbidities, No.	1.5 ± 1.2	1	1.8 ± 1.7	1	2.2 ± 1.8	2	1.7 ± 1.5	2	χ² = 2.3	3	.51
DUSOI score	37.1 ± 26.3	44	40.0 ± 24.4	44	44.9 ± 23.7	51	49.1 ± 24.5	54	χ² = 5.5	3	.14
Lifetime anxiety disorder, %	16		4		4		23		χ² = 10.9	3	.01
Lifetime substance use disorder, %	35		38		23		23		χ² = 3.8	3	.28
Baseline											
HDRS-17 score (only for participants who were depressed at entry, n = 98)	19.3 ± 4.9	17	20.6 ± 5.0	20	19.9 ± 4.7	18	18.4 ± 2.9	19	F = 0.9	3,94	.46
HDRS-25 score (only for participants who were depressed at entry, n = 98)	24.9 ± 5.6	24	27.6 ± 5.3	28	26.4 ± 4.6	26	23.7 ± 4.5	23	F = 2.4	3,94	.07
Bech-Rafaelsen score (only for participants who were manic or mixed at entry, n = 77)	20.8 ± 13.3	20	19.8 ± 11.4	22	22.0 ± 10.0	22	23.9 ± 11.1	26	F = 0.5	3,73	.67
GAF score	50.2 ± 9.8	52	47.8 ± 8.3	50	48.2 ± 7.2	50	46.6 ± 10.4	50	F = 1.2	3,170	.32
Polarity at study entry									χ² = 7.1	6	.31
Depressed, %	63		47		65		49				
Manic, %	23		40		31		38				
Mixed or cycling, %	14		13		4		13				
Duration of index episode, wk	42.5 ± 53.7	21	34.2 ± 66.9	20	30.6 ± 44.5	15	34.6 ± 64.8	19	χ² = 2.0	3	.57
Previous depressive episodes, No.		5		4		4		4	χ² = 0.2	3	.99
Previous manic episodes, No.		4		3		3		3	χ² = 2.6	3	.45
Age at first depressive episode, y	23.6 ± 7.3	21	20.9 ± 6.9	19	21.3 ± 7.4	20	23.2 ± 9.5	21	F = 1.2	3,160	.32
Age at first manic episode, y	25.3 ± 8.2	23	25.3 ± 9.2	21	26.1 ± 9.8	22	27.2 ± 9.3	26	F = 0.4	3,169	.78

Abbreviations: DUSOI, Duke Severity of Illness Checklist; GAF, Global Assessment of Functioning; HDRS, Hamilton Depression Rating Scale; ICM/ICM, intensive clinical management during both the acute and maintenance phases; ICM/IPSRT, ICM during the acute phase and interpersonal and social rhythm therapy (IPSRT) during the maintenance phase; IPSRT/ICM, IPSRT during the acute phase and ICM during the maintenance phase; IPSRT/IPSRT, IPSRT during both the acute and maintenance phases.

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=3.02, P=.003, hazard ratio, 3.11). We also observed significant interactions between assignment to IPSRT and medical burden and lifetime anxiety disorders, such that those subjects receiving IPSRT who had few inactive medical problems had longer survival times, but those with more medical problems 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 (F₃,₁₁₂=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 (F₃,₁₂₁=0.42, P=.74). After controlling for marital status, medical comorbidity, and anxiety history, there still was no difference among the treatment conditions (F₃,₁₁₇=0.46, P=.71); 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.[54] 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-

Table 2. Time to First Affective Episode in the Maintenance Phase as a Function of Acute Treatment Assignment: Survival Model After Stepwise Selection Procedure*

Effect	Parameter Estimate ± SE	Hazard Ratio	z	P Value
Acute-phase IPSRT	−1.09 ± 0.42	0.34	−2.58	.01
Acute-phase IPSRT: anxiety disorder	1.72 ± 0.62	5.61	2.76	.006
ICM: anxiety disorder	0.06 ± 0.64	1.06	0.09	.93
Acute-phase IPSRT: inactive medical comorbidities	0.33 ± 0.13	1.39	2.62	.009
ICM: inactive medical comorbidities	−0.18 ± 0.12	0.84	−1.50	.13
Active medical comorbidities	0.11 ± 0.07	1.12	1.66	.10
Married	−1.40 ± 0.39	0.25	−3.58	<.001
Index episode manic	0.34 ± 0.35	1.40	0.95	.34
Index episode mixed	1.14 ± 0.38	3.11	3.02	.003

Abbreviations: ICM, intensive clinical management; IPSRT, interpersonal and social rhythm therapy.
*Model fit, R^2 = 0.23; likelihood ratio test, χ^2 = 32.3; df = 9; P<.001.

cial routines, we used the fitted values for patient acute-phase SRM score at time of remission from this mixed-effects model as a covariate in a logistic regression for likelihood of recurrence. We used the fitted scores rather than the actual ones because the SRM scores exhibited high within-subject variability and not every subject had an SRM score corresponding precisely to the point of remission. Higher fitted SRM score at remission was predictive of lower probability of recurrence (P=.05) when controlling for acute-phase randomization. Thus, acute-phase IPSRT is associated with increasing SRM scores and reduced probability of recurrence. These 2 results taken together suggest that increased regularity of daily routines is a mediator of the effect of acute-phase IPSRT on likelihood of recurrence.[55,56]

To further explore the effect of treatment on SRM scores, we employed functional principal components analysis[57] to examine patterns of change in SRM scores during the acute and maintenance treatment phases. We used functional principal components analysis rather than change scores because, consistent with the IPSRT manual, many participants did not begin to complete the SRM until several weeks after treatment began and, again, because SRM scores exhibited large within-subject variability. Functional principal components analysis deals with these problems by first smoothing the data for each subject and then using the smoothed values as the basis for further analysis.

Among participants treated with ICM, the first principal component (accounting for 75% of large-scale variation) describes patients with slightly more variation in scores over the acute phase. However, among those treated with IPSRT, the first principal component (accounting for 85% of large-scale variation) is one that describes patients with consistently higher or lower SRM scores over the acute phase. This first principal component begins at approximately the same level of regularity as that observed in the ICM subjects but quickly rises to a higher level and remains there for the rest of the acute phase (**Figure 3**).

COMMENT

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[25,26] 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-
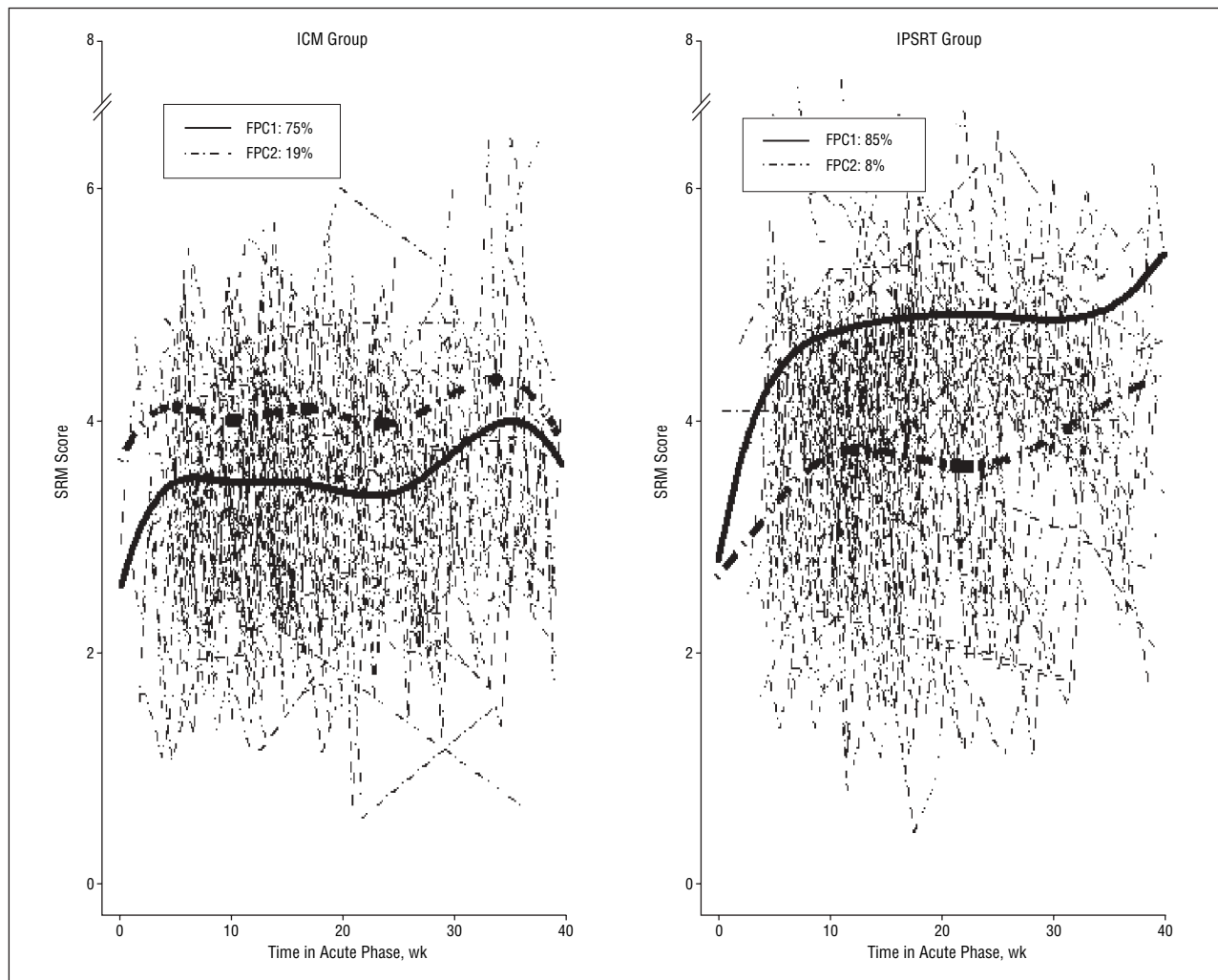
Figure 3. Functional principal components (FPCs) of the Social Rhythm Metric (SRM) score over the course of acute treatment for subjects receiving intensive clinical management (ICM) and interpersonal and social rhythm therapy (IPSRT).

chotherapy 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[58,59] and half have not.[60,61]

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,[62-64] 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.

Participants 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.[65] 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.[66]

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.[1,46] 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.

REFERENCES

1. Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, Cole K, Lavelle J. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. *N Engl J Med.* 1989;321:1489-1493.
2. Harrow M, Goldberg JF, Grossman LS, Meltzer HY. Outcome in manic disorders: a naturalistic follow-up study. *Arch Gen Psychiatry.* 1990;47:665-671.
3. Maj M, Pirozzi R, Kemali D. Long-term outcome of lithium prophylaxis in patients initially classified as complete responders. *Psychopharmacology (Berl).* 1989;98:535-538.
4. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry.* 1990; 47:1106-1111.
5. Markar HR, Mander AJ. Efficacy of lithium prophylaxis in clinical practice. *Br J Psychiatry.* 1989;155:496-500.
6. Shapiro DR, Quitkin FM, Fleiss J. Response to maintenance therapy in bipolar illness: effect of index episode. *Arch Gen Psychiatry.* 1989;46:401-405.
7. Prien RF, Potter WZ. *Psychopharmacol Bull.* 1990;26:409-427 NIMH workshop report on treatment of bipolar disorder.
8. Perry A, Tarrier N, Morriss R, McCarthy E, Limb K. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *Br Med Bull.* 1999;318:149-153.
9. Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea JM, Benabarre A, Torrent C, Comes M, Corbella B, Parramon G, Corominas J. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Arch Gen Psychiatry.* 2003;60: 402-407.
10. Simon GE, Ludman E, Unuetzer J, Bauer MS. Design and implementation of a randomized trial evaluating systematic care for bipolar disorder. *Bipolar Disord.* 2002;4:226-236.
11. Simon GE, Ludman EJ, Unutzer J, Bauer MS, Operskalski B, Rutter C. Randomized trial of a population-based care program for people with bipolar disorder. *Psychol Med.* 2005;35:13-24.
12. Bauer MS, McBride L. *Structured Group Psychotherapy for Bipolar Disorder: The Life Goals Program.* New York, NY: Springer Publishing Co, Inc; 1996.
13. Beck AT, Rush AJ, Shaw BF, Emery G. *Cognitive Therapy of Depression.* New York, NY: Guilford Press; 1979.
14. Lam DH, Jones SH, Hayward P, Bright JA. *Cognitive Therapy for Bipolar Disorder.* Chichester, United Kingdom: John Wiley & Sons, Ltd; 1999.
15. Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, Parr-Davis G, Sham P. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. *Arch Gen Psychiatry.* 2003; 60:145-152.
16. Lam DH, Hayward P, Watkins ER, Wright K, Sham P. Relapse prevention in pa-

tients with bipolar disorder: cognitive therapy outcome after 2 years. *Am J Psychiatry*. 2005;162:324-329.

17. Scott J, Garland A, Moorhead S. A pilot study of cognitive therapy in bipolar disorders. *Psychol Med*. 2001;31:459-467.

18. Miklowitz DJ, Goldstein MJ. *Bipolar Disorder: A Family-Focused Treatment Approach*. New York, NY: Gilford Press; 1997.

19. Miklowitz DJ, Goldstein MJ. Behavioral family treatment for patients with bipolar affective disorder. *Behav Modif*. 1990;14:457-489.

20. Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Arch Gen Psychiatry*. 2003;60:904-912.

21. Rea MM, Tompson M, Miklowitz DJ, Goldstein MJ, Hwang S, Mintz J. Family-focused treatment versus individual treatment for bipolar disorder: results of a randomized clinical trial. *J Consult Clin Psychol*. 2003;71:482-492.

22. Frank E, Kupfer DJ, Ehlers CL, Monk TH, Cornes CL, Carter S, Frankel DR. Interpersonal and social rhythm therapy for bipolar disorder: integrating interpersonal and behavioral approaches. *Behavior Therapist*. 1994;17:143-149.

23. Klerman GL, Weissman MM, Rounsaville BJ, Chevron ES. *Interpersonal Psychotherapy of Depression*. New York, NY: Basic Books Inc; 1984.

24. Weissman M, Markowitz J, Klerman G. *A Comprehensive Guide to Interpersonal Psychotherapy*. New York, NY: Basic Books Inc; 2000.

25. Ehlers CL, Frank E, Kupfer DJ. Social zeitgebers and biological rhythms: a unified approach to understanding the etiology of depression. *Arch Gen Psychiatry*. 1988;45:948-952.

26. Ehlers CL, Kupfer DJ, Frank E, Monk TH. Biological rhythms and depression: the role of zeitgebers and zeitstorers. *Depression*. 1994;1:285-293.

27. Malkoff-Schwartz S, Frank E, Anderson BP, Hlastala SA, Luther JF, Sherrill JT, Houck PR, Kupfer DJ. Social rhythm disruption and stressful life events in the onset of bipolar and unipolar episodes. *Psychol Med*. 2000;30:1005-1016.

28. Malkoff-Schwartz S, Frank E, Anderson B, Sherrill JT, Siegel L, Patterson D, Kupfer DJ. Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes: a preliminary investigation. *Arch Gen Psychiatry*. 1998;55:702-707.

29. Elkin I, Shea MT, Watkins JT, Imber SD, Sotsky SM, Colins JF, Glass DR, Pilkonis PA, Leber WR, Docherty JP, Fiester SJ, Parloff MB. National Institute of Mental Health Treatment of Depression Collaborative Research Program: general effectiveness of treatments. *Arch Gen Psychiatry*. 1989;46:971-982.

30. Spitzer R, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry*. 1978;35:773-782.

31. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.

32. Bech P, Bolwig TG, Kramp P, Rafaelsen OJ. The Bech-Rafaelsen Mania Scale and the Hamilton Depression Scale. *Acta Psychiatr Scand*. 1979;59:420-430.

33. Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry*. 1978;35:837-844.

34. First MB, Gibbon ML, Spitzer RL, Williams JBW. *Structured Clinical Interview for DSM-IV (SCID-1): User's Guide and Interview, Research Version*. New York, NY: Biometrics Research Department, New York Psychiatric Institute; 1995.

35. Thase ME, Carpenter L, Kupfer DJ, Frank E. Clinical significance of reversed vegetative subtypes of recurrent major depression. *Psychopharmacol Bull*. 1991;27:17-22.

36. Parkerson GR, Broadhead E, Tse CK. The Duke Severity of Illness Checklist (DUSOI) for measurement of severity and comorbidity. *J Clin Epidemiol*. 1993;46:379-393.

37. Monk TH, Flaherty JF, Frank E, Hoskinson K, Kupfer DJ. The Social Rhythm Metric (SRM): an instrument to quantify the daily rhythms of life. *J Nerv Ment Dis*. 1990;178:120-126.

38. Frank E, Kupfer DJ, Thase ME. New psychopharmacologic and psychotherapeutic strategies for long-term treatment of mood disorders. In: Costa E, Silva JA, Nadelson CC, eds. *International Review of Psychiatry*. Washington, DC: American Psychiatric Press; 1993:161-184.

39. Monk TH, Petrie SR, Hayes AJ, Kupfer DJ. Regularity of daily life in relation to personality, age, gender, sleep quality and circadian rhythms. *J Sleep Res*. 1994;3:196-205.

40. Frank E, Kupfer DJ, Wagner EF, McEachran A, Cornes C. Efficacy of interpersonal psychotherapy as a maintenance treatment for recurrent depression: contributing factors. *Arch Gen Psychiatry*. 1991;48:1053-1059.

41. Wagner E, Frank E, Steiner S. Discriminating maintenance treatments for recurrent depression: development and implementation of a rating scale. *J Psychother Pract Res*. 1992;1:280-290.

42. Frank E. *Treating Bipolar Disorder: A Clinician's Guide to Interpersonal and Social Rhythm Therapy*. New York, NY: Guilford Press; 2005.

43. Frank E. Interpersonal psychotherapy as a maintenance treatment for patients with recurrent depression. *Psychotherapy*. 1991;28:259-266.

44. Fawcett J, Epstein P, Fiester SJ, Elkin I, Autry JH. Clinical management—imipramine/placebo administration manual: NIMH Treatment of Depression Collaborative Research Program. *Psychopharmacol Bull*. 1987;23:309-324.

45. Frank E, Kupfer DJ, Perel JM, Cornes CL, Jarrett D, Mallinger A, Thase M, McEachran AB, Grochocinski VJ. Three-year outcomes for maintenance therapies in recurrent depression. *Arch Gen Psychiatry*. 1990;47:1093-1099.

46. Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. *Arch Gen Psychiatry*. 1984;41:1096-1104.

47. Hogarty GE, Anderson CM, Reiss DJ, Kornblith SJ, Greenwald DP, Javna CP, Madonia MJ; EPICS Research Group. Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia: I. One-year effects of a controlled study on relapse and expressed emotion. *Arch Gen Psychiatry*. 1986;43:633-642.

48. Leff J, Kuipers L, Berkowitz R, Eberlein-Vries R, Sturgeon D. A controlled trial of social intervention in the families of schizophrenic patients. *Br J Psychiatry*. 1982;141:121-134.

49. Falloon IRH, Boyd JL, McGill CW, Razoni J, Moss HB, Gilderman HA. Family management in the prevention of exacerbation of schizophrenia. *N Engl J Med*. 1982;306:1437-1444.

50. Tarrier N, Barrowclough C, Vaughn C, Bamrak JS, Porceddu K, Watts S, Freeman H. The community management of schizophrenia: a controlled trial of a behavioural intervention with families to reduce relapse. *Br J Psychiatry*. 1988;153:532-542.

51. Leff J, Berkowitz R, Shavit N, Strachan A, Glass I, Vaughn C. A trial of family therapy. V. A relatives group for schizophrenia. *Br J Psychiatry*. 1989;154:58-66.

52. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria; 2004.

53. SAS Institute Inc. SAS OnlineDoc, Version 8. Cary, NC: SAS Institute Inc; 2000.

54. Diggle PJ, Kenward MG. Informative drop-out in longitudinal data analysis (with discussion). *Appl Stat*. 1994;43:49-93.

55. Kraemer HC, Stice E, Kazdin A, Offord D, Kupfer DJ. How do risk factors work together? Mediators, moderators, and independent, overlapping and proxy risk factors. *Am J Psychiatry*. 2001;158:848-856.

56. Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry*. 2002;59:877-883.

57. Ramsay JO, Silverman BW. *Functional Data Analysis*. New York, NY: Springer-Verlag; 1997.

58. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, Markowitz JC, Nemeroff CB, Russell JM, Thase ME, Trivedi MH, Zajecka J. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med*. 2000;342:1462-1470.

59. de Jonghe F, Kool S, van Aalst G, Dekker J, Peen J. Combining psychotherapy and antidepressants in the treatment of depression. *J Affect Disord*. 2001;64:217-229.

60. Browne G, Steiner M, Roberts J, Gafni A, Byrne C, Dunn E, Bell B, Mills M, Chalklin L, Wallik D, Kraemer J. Sertraline and/or interpersonal psychotherapy for patients with dysthymic disorder in primary care: 6-month comparison with longitudinal 2-year follow-up of effectiveness and costs. *J Affect Disord*. 2002;68:317-330.

61. Ravindran AV, Anisman H, Merali Z, Charbonneau Y, Telner J, Bialik RJ, Weins A, Ellis J, Griffiths J. Treatment of primary dysthymia with group cognitive therapy and pharmacotherapy: clinical symptoms and functional impairments. *Am J Psychiatry*. 1999;156:1608-1617.

62. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34-38 years. *J Affect Disord*. 2002;68:167-181.

63. Kilbourne AM, Cornelius JR, Han X, Pincus HA, Shad M, Salloum I, Conigliaro J, Haas GL. Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord*. 2004;6:368-373.

64. Sharma R, Markar HR. Mortality in affective disorder. *J Affect Disord*. 1994;31:91-96.

65. Frank E, Cyranowski JM, Rucci P, Shear MK, Fagiolini A, Thase ME, Cassano GB, Grochocinski VJ, Kostelnik B, Kupfer DJ. Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. *Arch Gen Psychiatry*. 2002;59:905-912.

66. Cyranowski JM, Frank E, Shear MK, Swartz H, Fagiolini A, Scott J, Kupfer DJ. Interpersonal psychotherapy for depression with panic spectrum symptoms: a pilot study. *Depress Anxiety*. 2005;21:140-142.