Adjunctive Psychotherapy for Bipolar Disorder
Effects of Changing Treatment Modality

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ABSTRACT

In a randomized, controlled trial, the authors studied an adjunctive, individual psychotherapy, interpersonal and social rhythm therapy (IPSRT) for bipolar disorder. After stabilizing participants with episode appropriate pharmacotherapy and either IPSRT or intensive clinical management (CM), participants were reassigned to IPSRT or CM in conjunction with pharmacotherapy for 2 years of preventative treatment. Early results (n = 82) suggest that altering participants' treatment assignment at entry to the preventative phase is related to risk of recurrence. Participants remaining in the same treatment for both acute and preventative phases had lower rates of recurrence (<20% vs. >40%) and levels of symptomatology over the subsequent 52 weeks than those reassigned to the alternate modality. This finding, consistent with the authors' philosophy that bipolar patients benefit from stable routines, suggests that disruptions in the psychosocial treatment plan contribute to worse outcomes.

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Prior to the availability of lithium carbonate, psychotherapy was, ipso facto, a cornerstone of treatment for bipolar disorder. Early practitioners acknowledged the difficulties of conducting insight-oriented psychotherapy with this patient population (cf. Fromm-Reichmann, 1949), but
treatment alternatives (e.g., neuroleptics, sedatives, electroconvulsive therapy) were limited and generally inadequate. The development of lithium as a specific treatment for bipolar disorder in the 1950s ushered in an era of hope. Widespread use of pharmacotherapy, new data on the genetics of the illness, and prior psychotherapeutic failures contributed to a medicalization of the disorder and concomitant shift in treatment and research focus from the difficult psychological issues facing patients to allegedly treatment-amenable biological processes (Scott, 1995). Lithium was erroneously heralded as a "cure" for the disorder (Kupfer & Frank, 1997).

Early clinical trials documented the prophylactic efficacy of lithium (Baasstrup, Poulsen, Schou, Thomsen, & Amdisen, 1970; Prien, Caffey, & Klett, 1973), giving rise to undue expectations of lithium's capacity to prevent relapse in this population (Schou, 1997). A recent and growing body of literature, however, underscores lithium's limitations as a maintenance therapy. Satisfactory prophylactic lithium response over a 2-year period has been estimated from 33% (Prien et al., 1984) to 36% (Gelenberg et al., 1989) in rigorous clinical trials. In a naturalistic follow-up study, approximately 60% of participants continued to experience impaired psychosocial functioning 4 years after an index episode (Goldberg, Harrow, & Grossman, 1995). Coryell et al. (1993) observed that, for many bipolar patients, multiple psychosocial impairments persist at a 5-year follow-up, despite remission of clinical symptoms.

Experts debate the apparent decline in efficacy of lithium over 4 decades. Some investigators attribute lithium failure to inadequate compliance, dosing, and education in "carelessly selected" patients (Schou, 1997). Others suggest that a more heterogeneous patient sample (Gershon & Soares, 1997), increased comorbid substance abuse (Brady & Sonne, 1995), and lithium treatment of poorly responsive states such as dysphoric mania or rapid cycling (Keller, 1988) contribute to an impression of less favorable lithium outcomes. Regardless of etiology, a 1994 National Institute of Mental Health workshop on bipolar disorder concluded that it "is clear that pharmacotherapy alone does not meet the needs of many bipolar patients. Even with adequate medication treatment, many patients fail to show full recovery from acute episodes and display symptomatic and functional deficits during the interepisode period" (Prien & Rush, 1996, p. 217). Psychosocial treatments that augment pharmacotherapy, address the complex psychological sequelae of this recurrent disorder, and improve treatment adherence may ultimately mitigate the disappointing outcomes described with lithium prophylaxis alone (Goodwin & Jamison, 1990).

Scott (1995), Roth and Fonagy (1996), and Miklowitz and Frank (1999) have recently reviewed outcome data on psychotherapeutic approaches to bipolar disorder. All concluded that although methodologically sound treatment studies are sparse, the evidence suggests that psychosocial interventions benefit bipolar patients. Described treatment approaches include family therapy (e.g., Clarkin et al., 1990; Miklowitz & Goldstein, 1990), group therapy (e.g., Cerbone, Mayo, Cuthbertson, & O'Connell, 1992; Van Gent & Zwart, 1994), and individual therapy. In the last category, the literature includes one case series of 24 patients treated with psychodynamically oriented individual psychotherapy (Benson, 1975) and a randomized, controlled trial of a brief (6-session) course of cognitive therapy developed to improve medication adherence (Cochran, 1984). As described below, our group has developed interpersonal and social rhythm therapy (IPSRT; Frank et al., 1994), an interpersonally focused individual psychotherapy that incorporates behavioral and environmental interventions to help stabilize irregularities of the sleep—wake cycle that are presumed to be involved in the genesis of bipolar episodes.

IPSRT is built on the principles of interpersonal therapy (IPT) developed by Klerman, Weissman, Rounsaville, & Chevron (1984), strongly influenced by Goodwin and Jamison's (1990) "instability"
model of bipolar illness, and shaped by our own theories about the role of social and environmental "Zeitstörers" (time disturbers) in the development of affective episodes (Ehlers, Kupfer, Frank, & Monk, 1993). Goodwin and Jamison's model predicts three likely routes to recurrence in bipolar patients maintained on medication: (a) stressful life events, (b) disruptions in social rhythms, and (c) medication noncompliance. IPSRT targets each of these potential pathways to illness.

In IPSRT, like traditional IPT, patients are taught to recognize the relationship between mood and life events. One of four possible IPT problem areas (grief, interpersonal role transition, role dispute, or interpersonal deficits) is identified as the treatment focus, and the strategies outlined by Klerman et al. (1984) are used to help patients solve their interpersonal problems. As per the Goodwin and Jamison (1990) model and the social zeitgeber hypothesis, IPT's focus on mood and life events is amplified in IPSRT to include scrupulous attention to the disruptive effects that interpersonal difficulties can have on daily routines and the subsequent mood perturbations that result from these changes. The Social Rhythm Metric (SRM; Monk et al., 1990), a self-report form to record daily activities, is an integral part of IPSRT. Working from the SRM, patients learn to monitor routines and strive for lifestyle regularity (Frank et al., 1997). Psychoeducation helps patients learn about bipolar disorder and their medications, thereby decreasing denial and improving adherence to pharmacotherapeutic regimens. Ancillary family education sessions help with this process. Perhaps more important, patients are provided with an affectively meaningful forum in which to explore feelings about both the need for medication and the impact of illness on their quality of life or expected life trajectory. In summary, IPSRT is designed to help patients maximize the regularity of daily routines, adhere to medication regimens, better manage affective symptoms, and resolve interpersonal problems that relate to the onset and persistence of an affective episode.

This report presents early findings from an ongoing, randomized trial comparing IPSRT with intensive clinical management as adjunctive maintenance treatments for bipolar disorder. The study is designed to test relative efficacies of IPSRT and clinical management as maintenance therapies in bipolar disorder. Soon after the study began, however, we observed a deterioration in many patients who, by study design, changed psychosocial treatments after they had stabilized. Patients whose psychotherapy did not change seemed to fare better. In keeping with prior observations that change can precipitate a bipolar episode (Goodwin & Jamison, 1990), we hypothesized that changing psychosocial treatments is deleterious to bipolar patients.

**Method**

**Study Design**

The Maintenance Therapies in Bipolar Disorder protocol is an ongoing randomized clinical trial conducted at the University of Pittsburgh testing the efficacy of IPSRT as an adjunctive maintenance treatment for bipolar 1 disorder. Participants are enrolled in the protocol during an acute affective episode (see below) and randomly assigned to acute phase treatment with either IPSRT or intensive clinical management (CM). Participants are reassigned to either IPSRT or CM for preventative treatment.

Protocol pharmacotherapy begins with lithium, but neuroleptics, benzodiazepines, antidepressants, and other mood stabilizers can be used alternatively or adjunctively according to a specified algorithm that is available from the authors on request. Generally, in the acute phase of treatment, patients are started on a mood stabilizer alone. Lithium monotherapy is encouraged, but patients who do not respond to lithium, cannot tolerate lithium, or whose medical history precludes lithium may be
given sodium divalproex or carbamazepine. Perphenazine, olanzapine, and lorazepam are used adjunctively to manage manic symptoms. Phenelzine or paroxetine can be added if depressive symptoms do not respond to therapeutic levels of a mood stabilizer. Once a patient is stabilized, all medications except the mood stabilizer are slowly withdrawn in preparation for entering the preventative phase of treatment. If individuals cannot tolerate monotherapy with a mood stabilizer, they enter the preventative phase on the combination of medications that led to stabilization. Pharmacotherapy remains unchanged from the point of reassignment forward. When prodromal symptoms of mania are observed, neuroleptics may be used as "rescue" medication for a period limited to 5 days. Prodromal depressive symptoms are not treated pharmacologically. Pharmacotherapy guidelines are constant across both treatment conditions.

After the patient achieves a stable remission on a constant medication regimen for 4 weeks (a calculated average of the 17-item version of the Hamilton Rating Scale for Depression [HRSD; Hamilton, 1960] and Bech-Rafaelsen Mania Scale [Bech, Bolwig, Kramp, & Rafaelson, 1979]), he or she is reassigned to either CM or IPSRT for the preventative phase. The patient continues to see the same therapist, regardless of treatment reassignment. Preventative treatment consists of biweekly sessions for 12 weeks followed by monthly sessions for 2 years. Because participants are randomly assigned in both the preliminary and preventative phases, four possible treatment combinations emerge: (a) acute IPSRT followed by preventative IPSRT (IPSRT/IPSRT); (b) acute IPSRT followed by preventative CM (IPSRT/CM); (c) acute CM followed by preventative CM (CM/CM); and (d) acute CM followed by preventative IPSRT (CM/IPSRT).

**Participants**

Participants eligible for inclusion in the study are between the ages of 21 and 65, meet Schedule for Affective Disorders and Schizophrenia criteria (Endicott & Spitzer, 1978) and Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978) for bipolar I disorder, and are in the midst of at least their third discrete affective episode. The offset of the most proximal previous episode must have occurred less than 5 years prior to the onset of the index episode, and the current episode must meet severity criteria (HRSD-17 >= 15 or Bech-Rafaelsen >= 15). Exclusion criteria include current rapid cycling (>= 4 affective episodes per year), chronic drug or alcohol abuse (unless confined to affective episodes), pregnancy, and significant medical illness that would preclude protocol pharmacotherapy. Participants who met criteria for schizophrenia, borderline personality disorder, or antisocial personality disorder are also excluded from the study. However, we include in this sample 12 participants who did not meet full inclusion/exclusion criteria (4 had only a single episode of mania; 2, with no prior treatment, had no clear-cut periods of remission; 2 were treated initially with medications other than lithium; 1 met criteria for rapid cycling; 1 met criteria for schizoaffective disorder; and 2 had last episodes >5 years ago). These 12 participants were randomized separately at entry to the study but were otherwise subject to all protocol requirements.

After giving written, informed consent, participants were randomly assigned to treatment as described above. This analysis included 82 participants who entered the preventative phase of treatment as of October 1, 1997. This group represented 65% (82/126) of all participants enrolled in the study as of October 1, 1997. The remaining 44 participants had either dropped out, been in the preliminary phase for <12 weeks, or were too symptomatic to have entered preventative treatment by the cut-off date. The 82 participants were evenly distributed across the four possible treatment conditions: IPSRT/IPSRT (n = 18); IPSRT/CM (n = 25); CM/CM (n = 22); and CM/IPSRT (n = 17).

**Treatments IPSRT.**
IPSRT has been described in some detail in an earlier report (Frank et al., 1994). Briefly, IPSRT is a manual-based psychotherapy focusing on (a) the link between mood and life events; (b) the importance of maintaining regular daily rhythms, as elucidated by the SRM; (c) the identification and management of potential precipitants of rhythm dysregulation, with special attention to interpersonal triggers; (d) the facilitation of mourning the lost healthy self; and (e) the identification and management of affective symptoms. The stance of the therapist is warm, supportive, and active.

Treatment is divided into four stages. In the initial phase, conducted over 4—5 weekly sessions, the therapist collects a thorough psychiatric and medical history, diagnoses the patient with bipolar disorder, conducts an assay of all important individuals in the patient's life (the interpersonal inventory), initiates the SRM, identifies the treatment focus (an interpersonal problem area), and educates the patient about the role and importance of medication. In the intermediate phase, conducted weekly over several weeks to months, the therapist helps the patient develop strategies to resolve the interpersonal problem area, stabilize daily rhythms, and manage affective symptoms. The therapist also provides a forum for the patient to mourn lost "highs," struggle with denial, and find a balance between spontaneity and stability. In the preventative phase, treatment frequency decreases to monthly and lasts 2 years. The patient is provided with an opportunity to consolidate treatment gains and increase confidence in his or her capacity to apply these techniques outside of sessions. The final phase of treatment facilitates termination of the research psychotherapy. The therapist reviews treatment successes as well as patient vulnerabilities, helping the patient identify strategies for future management of interpersonal difficulties and symptom flares. Termination is handled gradually, occurring over 4—6 monthly sessions.

CM.

CM is modeled on—but more intensive than—the briefer visits conducted in medication clinic settings. The stance of the therapist is warm and empathic, but treatment focuses on symptoms, patient education, medication adherence, and management of side effects. CM neither offers the patient a psychosocial model of illness nor provides strategies for addressing interpersonal conflicts. CM patients are asked to fill out the SRM for research purposes, but its contents are not discussed with the therapist, and no effort is made to regularize social rhythms. In a prior trial conducted by our group, a similar form of clinical management (plus placebo) had a low rate of attrition over a 3-year period, yet a significantly lower rate of prophylaxis when compared with the IPT (±placebo) conditions (Frank et al., 1990).

Although conceptualized as a control condition, we have come to think of CM as a nonspecific, "low-dose" psychotherapy in contrast to the more intensive, "high-dose" psychotherapy, IPSRT (Frank et al., 1990). In CM, highly skilled and empathic clinicians offer considerable support, education, and practical advice to the patient, within the constraint of not providing IPSRT interventions. It is incorrect to assume that CM represents an inactive, placebo condition.

Both IPSRT and CM are administered weekly in the preliminary phase and then tapered to biweekly and then monthly sessions in the preventative phase. The maximum number of sessions in the preliminary phase is not fixed in either condition, although participants must complete a minimum of 12 preliminary phase therapy visits before moving to the preventative phase. Most participants then receive 6 biweekly sessions followed by 21 monthly visits during the 2-year preventative phase. Participants who move from CM in the preliminary phase to IPSRT in the preventative phase are given 3 extra weekly sessions in the preventative phase to initiate IPSRT treatment. CM sessions are
half as long as IPSRT sessions (20 vs 45 min duration). In both treatments, patients see both a therapist and a physician at each visit.

**Outcome Measures**

Participants are assessed at each visit by an independent evaluator who is unaware of the participant's treatment assignment. Depressive symptoms are rated on both the 17-item version of the HRSD and a 25-item version developed by our group to rate reverse neurovegetative symptoms (Thase, Carpenter, Kupfer, & Frank, 1991). Manic symptoms are assessed with the 12-item Bech-Rafaelsen Mania Scale. Interrater reliability for the HRSD (25 item) and Bech-Rafaelson were acceptable, with interclass coefficients of 0.92 and 0.93, respectively. Recurrence is declared when a patient meets RDC criteria for a major depressive episode or manic episode accompanied by 17-item HRSD or Bech-Rafaelson score >=15 at two consecutive visits or, if hospitalized, at a single visit. All suspected recurrences are evaluated and confirmed by an independent, senior psychiatrist unaware of the participant's treatment assignment. Lithium, valproate, and carbamazepine blood levels are obtained at each clinic visit. Ratios of blood level to dose (L/D) were calculated by dividing the blood level by the previous week's prescribed medication dose.

**Data Analysis**

Univariate statistics were performed initially to determine the distribution of variables. When covariates were examined for possible influence on outcome, variables having skewed distributions (e.g., duration of index episode, age of onset of illness, etc.) were transformed using natural log transformation. Means and standard deviation for these variables, however, were reported in their original units. Analyses of variance (ANOVA) and repeated measures ANOVAs were used to analyze normally distributed, continuous data. The Wilcoxon rank sum test was used to compare continuous variables that were not normally distributed. Categorical variables were compared with chi-square tests. Kaplan-Meier survival analyses were used to determine time to recurrence. Dropouts were treated as censored data except where specified.

**Results**

Analyses were conducted on 82 participants who had successfully completed the acute phase and entered the preventative phase of treatment prior to a specified cut-off date (October 1, 1997).

**Demographic Information**

Demographic information is presented in Table 1. The study population included more women (65%, n = 53) than men (35%, n = 29) and more single, separated, or divorced individuals (63%, n = 52) than married individuals (37%, n = 30). Participants were predominantly Caucasian (94%, n = 77), well educated (79% had >=14 years of education), with a mean age at study entry of 36 (±10). Participants had median age at onset of first bipolar episode of 20 (range 13—51) and reported a median of 6 prior affective episodes (range 1—50). The median number of weeks spent in the preliminary phase of treatment was 32 (range 12—126). There were no significant differences in these demographic and clinical variables among participants assigned to the four treatment conditions (for all, p > .05).

**Risk of Recurrence Related to Psychosocial Treatment Assignment**
Survival analysis documented an overall risk of recurrence of 34% during the first year of preventative treatment. Although a comparison of the survival curves for the four treatment groups yielded no significant difference at 52 weeks, analyses suggested a trend toward differences among groups that might reach significance with a larger sample size (log-rank = 5.16, \( p = .16 \)). Mean number of weeks to recurrence was similar across treatment groups (36.6, 33.4, 32.1, and 37.1 in CM/CM, CM/IPSRT, IPSRT/CM, and IPSRT/IPSRT, respectively). Median number of weeks to recurrence was greater in the CM/CM and IPSRT/IPSRT groups (52.0 and 49.2, respectively) compared with CM/IPSRT and IPSRT/CM groups (38.1 and 37.0, respectively). Because we hypothesized that changing psychosocial treatments negatively affects outcome, we then collapsed the data to compare groups with altered versus stable treatment assignments. The recurrence hazard was highly related to the assignment to stable versus altered treatment. Specifically, only 7 out of 40 (17.5%) participants assigned to stable treatment (IPSRT/IPSRT or CM/CM) experienced a recurrence, compared with 17 out of 42 (40.5%) participants assigned to altered treatments (IPSRT/CM or CM/IPSRT), log-rank \( \chi^2 \) (1) = 4.66, \( p = .03 \) (see Figure 1). The group that “lost” psychotherapy (IPSRT/CM) and the group that “gained” it (CM/IPSRT) had comparable survival curves, as did the groups who received either psychotherapy or no psychotherapy in both phases (IPSRT/IPSRT or CM/CM; see Figure 1).

**Participants Surviving >=12 Weeks of Preventative Treatment**

Hypothesizing that the effects of altering treatment would be experienced acutely (i.e., soon after changing treatment modalities), we repeated our analyses with a subgroup of participants who survived at least 12 weeks of preventative treatment (\( n = 69 \)) as of a specified cut-off date (December 16, 1997). We speculated that these participants, having withstood the acute effects of changing treatment, would no longer show differential vulnerability to relapse. Contrary to our initial hypothesis, the increased risk of recurrence in participants with altered (IPSRT/CM or CM/IPSRT) versus stable (IPSRT/IPSRT or CM/CM) treatments tended to continue at 52 weeks, log-rank \( \chi^2 \) (1) = 3.62, \( p = .06 \). A visual inspection of the survival analyses (see Figure 1) suggests that the curves diverge around 25 weeks, further suggesting that the effect of changing treatments is not immediate.

**Subsyndromal Symptom Flurries**

Subsyndromal symptom flurries represent a clinically important parameter of bipolar illness (Keller et al., 1992). To assess relative symptom variability in the treatment conditions we are studying, we calculated average monthly symptom scores (determined by doubling the 12-item Bech-Rafaelsen score and adding it to the 25-item HRSD score at each clinic contact and then calculating monthly group averages) during the first 52 weeks of preventative treatment. We used average monthly scores because most participants were seen monthly in the preventative phase (i.e., stable patients), whereas other participants were seen more frequently (i.e., those who were deteriorating or in crisis). To capture both depressive and [hypo]manic symptoms, we created a composite score from reliable depression (HRSD) and mania (Bech-Rafaelsen) measures. Because there are half as many items in the mania scale, we doubled the raw Bech-Rafaelsen score, thus giving equal weight to depressive and [hypo]manic symptoms. Using a repeated measures ANOVA, we found that participants whose treatment changed (CM/IPSRT, IPSRT/CM) were marginally more symptomatic than participants in stable treatment (IPSRT/IPSRT, CM/CM), \( F \) (1, 831) = 3.68, \( p = .06 \), (see Figure 2). In individual group comparisons, participants who started out in IPSRT and then lost it (IPSRT/CM) had significantly higher scores than participants assigned to the three other treatment conditions: CM/CM, \( F \) (1, 805) = 7.32, \( p = .01 \); CM/IPSRT, \( F \) (1, 805) = 6.65, \( p = .01 \); and IPSRT/IPSRT, \( F \) (1, 805) =
4.63, \( p = .03 \). Within the group that survived at least 12 weeks after entering preventative treatment, there were no differences in average symptom scores between the stable and altered treatment groups, but comparisons of the four groups’ average symptom scores over 52 weeks of treatment indicated a significant main effect of group, \( F(3, 683) = 4.50, p < .01 \). Individual comparisons yielded significantly higher (worse) scores in the IPSRT/CM group relative to CM/CM, \( F(1, 683) = 5.98, p = .01 \), and CM/IPSRT, \( F(1, 683) = 12.28, p < .01 \). Curiously, in this 12-week survivor group, IPSRT/IPSRT average scores were significantly higher than IPSRT/CM scores, \( F(1, 683) = 4.01, p = .05 \).

**Other Possible Explanations for Differential Outcomes**

We considered other possible explanations for these interesting differences among the treatment conditions including changes in assigned clinicians, termination against medical advice (AMA), time in acute treatment (as a rough indicator of baseline severity), the predominant polarity of the episode treated in the preliminary treatment phase of this study, and medication adherence. In other words, were patients in the altered treatment conditions, either by chance or through some process associated with the change in treatment, more likely to have experienced a change in assigned clinician (necessitated by the clinician's departure from our clinic), to have prematurely left the study, to have a more severe form of the illness, or to have been less adherent to their medication regimen? As is detailed below, we found no significant relationships between any of these variables and treatment outcome, except predominant treatment polarity.

**Changes in assigned clinicians, termination AMA, and time in acute treatment.**

Thirty percent (25/82) of participants experienced a change in therapist or psychiatrist during the course of treatment, but change of assigned clinicians did not significantly affect risk for recurrence (Fisher's exact \( p = .61 \)). Termination AMA did not differ significantly (Fisher's exact \( p = .18 \)) by treatment condition: 3/22 (CM/CM), 1/17 (CM/IPSRT), 3/18 (IPSRT/IPSRT), 3/25 (IPSRT/CM). There was a trend for the number of weeks required to complete the preliminary phase to be associated with survival time in the 52-week analyses, log-rank \( \chi^2(1) = 2.94, p = .09 \), with more weeks in preliminary treatment associated with shorter survival times.

**Medication adherence.**

Medication adherence was evaluated in the subgroup (\( n = 78 \)) of participants who received lithium in the preventative phase (alone or in combination with other mood stabilizers). The number of participants taking other mood stabilizers instead of lithium (\( n = 4 \)) was too small to permit meaningful analyses. We evaluated lithium blood levels (mEq/L), level-to-dose (L/D) ratios, and coefficient of variation for the L/D ratios (calculated as the standard deviation divided by the mean L/D ratio multiplied by 100%, with a minimum of five values used to calculate this variable). The mean lithium blood level across treatment groups was 0.82 mEq/L (range 0.12—1.15) in the preventative phase, with no significant differences among treatment groups, \( F(3, 74) = .36, p = .78 \). There were no differences in lithium levels, L/D ratios, or coefficients of variation of L/D ratios between participants in the stable versus altered treatment conditions (for all, \( p > .05 \)). Comparisons of lithium levels in the 2 weeks before reassignment with the 2 weeks following reassignment with a repeated measures ANOVA again revealed no significant differences among treatment groups, \( F(3, 74) = 1.02, p = .39 \).

Thirty-two percent (26/82) of participants entered and were maintained in the preventative phase of
treatment on at least one medication (antidepressant, antipsychotic, or sedative) in addition to a mood stabilizer. There were no differences in adjunctive medication use across treatment conditions (Fisher's exact $p = .66$). Four participants briefly received "rescue" medications in the preventative phase (2 in CM/CM, 1 in CM/IPSRT, 1 in IPSRT/IPSRT).

**Polarity of episode.**

We have reported elsewhere that during the preventative phase patients who were treated acutely for a mixed/cycling episode were significantly more likely to experience a recurrence than patients treated for a manic or a depressive episode (Frank et al., 1998). Of note, clinical state at entry to the study (i.e., polarity of episode when they were initially evaluated in our clinic) was not significantly related to risk of recurrence (log-rank $= .42$, $p = .81$). Kaplan-Meier analyses (see Figure 3) that examine the interaction between changing psychosocial treatments and treatment polarity (defined as predominant polarity of the episode for which they were treated acutely) show a consistent negative effect of altering treatment within each episode type. Cox proportional hazards analyses that control for the effects of polarity demonstrated a consistently higher risk of recurrence in the groups receiving altered treatments, Wald $\chi^2 (1) = 5.01$, $p < .03$, irrespective of the polarity of the episode for which a participant was treated prior to entering the preventative phase.

**Participants Who Did Not Meet All Study Criteria**

Because of an uneven distribution of the 12 participants who did not meet all study entry criteria across the four treatment cells and a low number of recurrences (2/12), we were unable to analyze this group separately. Nine of the 12 participants were in the altered treatment groups, and most of them (7/9) remained well.

**Discussion**

Several interesting findings emerged from these early analyses. Most notably, a majority of our patients have remained relatively well or, at least, have not experienced a full syndromal recurrence. Although preliminary, our analyses suggest that both "high-dose" and "low-dose" psychotherapy (IPSRT and CM, respectively), in conjunction with medication, are associated with relatively good outcomes compared with those observed in recent studies (Frank et al., 1998). A strong correlate of both recurrence and higher levels of ongoing symptomatology in the absence of recurrence is a change of psychotherapeutic treatment modality. This phenomenon appears to be unrelated to a change of therapist or physician, baseline illness severity, terminations against medical advice, or medication adherence. These findings are particularly remarkable in light of the fact that, according to our protocol, patients change neither their therapist nor timing of appointments nor medications at the point of entry into the preventative phase; the only changes are the content of the sessions, the duration of the session, and the nature of the therapist's interventions.

From a clinical standpoint, however, the change is meaningful. A patient moving from IPSRT to CM will suddenly find that the therapist does not inquire about or address problems with significant relationships. The therapist no longer monitors daily rhythms or links symptoms to life events. Efforts to discuss interpersonal dilemmas are gently discouraged as the therapist maintains a focus on symptom management. A patient who had benefited from these interventions will no longer receive them. We should reiterate, however, that the therapist remains warm, engaging, and involved regardless of treatment assignment. Conversely, a patient who had achieved remission with a symptom-focused approach (CM) changes to IPSRT and is suddenly encouraged to explore...
interpersonal problems. The introduction of potentially disturbing, affectively rich material at this juncture of treatment may "stir up" a previously stable patient. Increased attention to social rhythms may inadvertently perturb a fragile system and destabilize a marginally compensated bipolar patient. In keeping with our theory that stabilizing routines encourages wellness in a population with bipolar disorder, it appears that a constant treatment regimen contributes to enhanced stability. By contrast, changing treatment parameters, even in the modest terms required for half of the patients in this protocol, may represent yet another destabilizing pathway to recurrence in bipolar disorder.

Our methods select for patients who have benefited from their initial treatment assignment: By definition, they must achieve a euthymic mood state in order to move into the preventative phase. Patients who remain in stable treatment continue with a modality that led to recovery from an episode of illness; by contrast, participants assigned to altered treatments are forced to give up that same effective treatment. These findings bring to mind the adage, "If it ain't broke, don't fix it." Patients with bipolar illness who are euthymic but marginally compensated may not be able to tolerate even minor changes in their milieu.

We considered several possible explanations for the unexpected finding that the effect of changing treatments persists beyond 12 weeks. As we discussed above, only patients who respond to acute treatment may enter preventative treatment. The initial treatment assignment is, therefore, the treatment of choice for these individuals. Thus, a participant who receives a different psychosocial intervention in the preventative phase may ultimately receive what is for him or her a less effective preventative treatment. Risk of recurrence increases over time, so failure of the alternate treatment modality to prevent recurrence may become more apparent over time (i.e., beyond 12 weeks). We also speculate that the persistent effect of changed treatment may relate to the protective effects of more frequent sessions. In the first 12 weeks of preventative treatment, participants are seen biweekly. After 12 weeks, participants are seen monthly. More frequent therapy contacts—regardless of content—may confer some protection against the detrimental effects of altering treatment.

Interestingly, a change in therapist or psychiatrist necessitated by a maternity leave or a clinician's departure from our clinic does not seem to have the same effect as changing treatment conditions. Because our participants are receiving treatment in a research setting in which they have regular contact with independent evaluators, administrative staff, physicians' assistants, and laboratory personnel in addition to their treatment team, they may be buffered to some degree from the effects of losing any single individual involved in their treatment. Because all participants receive treatment from both a physician and a nonphysician therapist the presence of one unchanging clinician may mitigate against the loss of the other member of the team. These findings may very well not generalize to the solo practitioner setting.

We report elsewhere that polarity of episode is significantly related to risk of recurrence (Frank et al., 1998). In these analyses, mixed/cycling individuals continue to have poorer outcomes than the purely depressed or manic groups. The effect of changing psychosocial interventions is apparent, however, within each of the three episode-type groups. In other words, changing psychosocial treatments is deleterious regardless of episode type, although overall outcomes remain relatively poor for individuals with mixed or cycling states. Although we would not deny the centrality of biology to this illness, we believe our findings support the hypothesis that psychosocial treatments also affect the course of illness.

We found that polarity of episode treated acutely was significantly related to risk of recurrence but that clinical state (polarity) at entry to the protocol was not. This discrepancy reflects the greater

difficulty we have experienced in bringing about stable remission of depressive symptomatology relative to manic symptomatology. Thus, the patient who enters the protocol in a manic episode and is treated to remission without a switch to depression appears to have a much more stable form of remission (in this case, both clinical state at entry and polarity of episode treated acutely would be defined as manic). By contrast, both those patients who enter the protocol depressed (defined as depressed at entry) and those who switch into depression (defined as manic at entry) require much longer to achieve a stable remission and, apparently, that remission remains somewhat unstable as they move into the preventative phase. In these latter examples, the primary polarity of episode treated acutely would be defined as depressed which is, apparently, the more relevant variable.

Among participants whose treatment changed, there were no significant differences in recurrence rates between participants who gained or lost IPSRT. However, participants who lost IPSRT experienced higher (worse) average monthly symptom scores than participants who gained IPSRT, remained in IPSRT, or never received IPSRT at all. These findings suggest that moving from a structured, rigorous, enriched psychotherapy to a less intense approach may be particularly destabilizing for individuals with bipolar disorder. Our data suggest that it is better to never receive IPSRT than to receive it and then have it discontinued. We also observed that in the 12-week survivor group, IPSRT/IPSRT average scores were significantly higher (worse) than IPSRT/CM scores. This apparently contradictory finding may be attributable to the exclusion of the more fragile IPSRT/CM participants from 12 week survivor analyses. In other words, if IPSRT/IPSRT helped prevent recurrences in moderately symptomatic individuals, 12-week survivor analyses would include these more symptomatic individuals. By contrast, symptomatic IPSRT/CM participants who had already experienced a recurrence would be excluded. The IPSRT/CM group might appear healthier because the most fragile participants were censored in these analyses while the IPSRT/IPSRT group might appear more symptomatic precisely because the intervention was more effective in preventing recurrence. The same issue is not relevant in the 52-week analyses because all patients are included regardless of recurrence status. As additional data accrue, it will be interesting to continue to examine the effects of differentially sequencing these treatments.

Differences in terminations AMA, although not statistically significant in a Kaplan-Meier survival analysis, are roughly twice as high in the stable group (7/40) compared with the altered treatment group (4/42). In fact, when we repeated the survival analyses using both recurrence and terminations AMA as endpoints ("failures"), the differences between the groups, which were significant when considering recurrences only, diminished and no longer achieved statistical significance at 52 weeks (p = .06). This finding suggests that although risk of recurrence is higher in the altered treatment group, risk of termination AMA may be higher in the stable group, particularly among those participants who had hoped to receive psychotherapy after they entered the preventative phase but found they were assigned to continue the CM condition. We will need to see if these findings persist when the study is completed. In the interim, we can report anecdotally that a subset of participants assigned to CM for the preliminary phase expressed a strong desire for the opportunity to receive intensive psychotherapy in the second phase of treatment. When they were reassigned to maintenance treatment without intensive psychotherapy (CM), they dropped out.

As described previously, 12 of the 82 participants did not meet all the study entry criteria but are nevertheless included in these analyses. Unfortunately, we were unable to analyze this group separately at this point in the study. Because most of these participants were assigned to the altered treatment groups and remained well, the inclusion of this group in the analyses would tend to weaken our findings of worse outcomes among those with altered treatments.
Although medication can be experienced as a relatively exogenous therapeutic force, psychotherapy offers the individual a set of internally mediated strategies to help manage bipolar illness. We have written elsewhere that "[it] is our clinical impression that one of the major appeals of the IPSRT approach is that it gives patients the sense that there is something they can do, beyond adherence to the medication regimen, to influence the course of their affective disorder" (Frank et al., 1997, p. 1172). Prevalent among bipolar patients is the belief that psychotherapy helps them. Our preliminary findings support their intuition. Although the proper sequencing of psychotherapeutic approaches requires further elucidation, our data suggest that many patients want—and benefit from—adjunctive psychotherapy. Those who remain in the CM condition (and remain well) are apparently those for whom the absence of intensive psychotherapy is not important to their continued wellness.

**Conclusion**

These early observations must be viewed with caution because the study is not yet complete, and we present data only from the first year of a 2-year protocol of maintenance treatment. Our impressions from these preliminary data, however, support our initial hypotheses: Instability contributes to morbidity in bipolar disorder, and treatment approaches that increase stability improve outcome. The admittedly unexpected finding that altered treatment—rather than the content of the treatment per se—affects risk for recurrence underscores the insidious effects of instability in this population. Consonant with the Goodwin and Jamison model (1990) and our initial hypotheses, these preliminary findings suggest that psychotherapy may augment the effects of pharmacotherapy in this population and further implicate instability as a primary mediator of outcome in bipolar disorder.

**References**


Frank, E., Thase, M. E., Kupfer, D. J., Houck, P. R., Mallinger, A. G. & Swartz, H. A. (1998). Early results from the Pittsburgh Study of Maintenance Therapies in Bipolar Disorder 1: Comparisons with prior controlled trials. (Unpublished manuscript, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine)


**Description of Patient Sample**

<table>
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<tr>
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Fifty-two week survival curves for four possible psychosocial treatment sequences (n = 82). Recurrence hazard was highly related to stable (IPSRT/IPSRT or CM/CM) versus altered (IPSRT/CM or CM/IPSRT) treatment assignment, log-rank $\chi^2(1) = 4.66$, $p = .03$. IPSRT = interpersonal and social rhythm therapy; CM = clinical management.

Average symptom scores for altered versus stable psychosocial treatments over 52 weeks of preventative care. Repeated measures analysis of variance shows that participants whose treatment changed (CM/IPSRT, IPSRT/CM) were marginally more symptomatic than participants in stable treatment (IPSRT/IPSRT, CM/CM), $F(1, 831) = 3.68$, $p = .06$. CM = clinical management; IPSRT = interpersonal and social rhythm therapy.
Relationship of polarity (defined as predominant episode type treated during the acute phase of the study) to survival curves for altered and stable psychosocial treatments during 52 weeks of preventative treatment.