Psychotherapy Alone and Combined With Medication as Treatments for Bipolar II Depression: A Randomized Controlled Trial

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ABSTRACT

Objective: Bipolar II disorder (BP-II) is associated with marked morbidity and mortality. Quetiapine, the treatment with greatest evidence for efficacy in BP-II depression, is associated with metabolic burden. Psychotherapy, a treatment with few side effects, has not been systematically evaluated in BP-II. This study compared psychotherapy plus placebo to psychotherapy plus pharmacotherapy as treatments for BP-II depression.

Methods: From 2010 to 2015, unmedicated adults (n = 92) with *DSM-IV-TR* BP-II depression were randomly assigned to weekly sessions of Interpersonal and Social Rhythm Therapy (IPSRT) plus placebo or IPSRT plus quetiapine and followed for 20 weeks.

Results: For primary outcomes, IPSRT + quetiapine yielded significantly faster improvement on 17-item Hamilton Depression Rating Scale ($F_{1,115.4} = 3.924$, $P = .048$) and greater improvement on Young Mania Rating Scale ($F_{58.5} = 4.242$, $P = .044$) scores. Both groups, however, improved significantly over time with comparable response rates (≥ 50% reduction in depression scores): 67.4% (62/92) in the entire sample, with no between-group differences. Those randomly assigned to their preferred treatment were 4.5 times more likely to respond (OR = 4.48, 95% CI = 1.20–16.77, $P = .026$). IPSRT + quetiapine assignment was associated with significantly higher body mass index over time ($F_{67.96} = 6.671$, $P = .012$) and rates of dry mouth (79% v. 58%; $\chi^2 = 4.0$, $P = .046$) and a trend toward more complaints of oversedation (100% vs 92%; $\chi^2 = 3.4$, $P = .063$).

Conclusions: IPSRT plus quetiapine resulted in greater symptomatic improvement but also more side effects than IPSRT alone. A subset of participants improved with IPSRT alone, although absence of an inactive comparator limits interpretation of this finding. Receipt of preferred treatment was associated with better outcomes. Harms, benefits, and preferences should be considered when recommending treatments for BP-II depression.

Trial Registration: ClinicalTrials.gov identifier: NCT01133821

J Clin Psychiatry
https://doi.org/10.4088/JCP.16m11027

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Bipolar II disorder affects 1.1% of the population[1] and is associated with high levels of morbidity and mortality. Characterized by multiple, protracted depressive episodes,[2] bipolar II disorder (BP-II) is at least as disabling as—some would suggest more disabling than—bipolar I disorder (BP-I).[3] Although little is known about optimal approaches to pharmacotherapy,[4] even less is known about the role of psychotherapy in the management of BP-II. Given the large side effect burden associated with medications used to treat BP-II[5,6] and limited evidence with respect to efficacy,[4] it is important to consider the potential role of psychotherapy, a treatment with few side effects. Many individuals suffering from BP-II struggle with issues that lend themselves to psychosocial remediation, including the challenges of differentiating hypomania from well periods, disordered daily routines, and the negative impact of illness on relationships and functioning.[7] Thus, psychotherapy may play an important role in management of BP-II.

Definitive studies of psychotherapy for BP-II have not been conducted. Trials testing interventions for bipolar disorder more broadly have included subsets of individuals diagnosed with BP-II, with results suggesting possible efficacy of combined psychotherapy and mood stabilizing medication for BP-II.[8–10] Whereas psychotherapy alone is contraindicated for BP-I, it may be appropriate for individuals with BP-II, who, by definition, are at low risk of experiencing fully syndromal manic episodes or psychosis[11] and may wish to avoid risks associated with pharmacotherapy.[7] Efficacy of psychotherapy monotherapy in BP-II is unknown, although we have previously demonstrated feasibility of this approach in 2 small trials.[12,13]

The present study sought to compare psychotherapy plus placebo to psychotherapy plus pharmacotherapy as treatments for BP-II depression. We evaluated Interpersonal and Social Rhythm Therapy (IPSRT),[14] an evidence-based psychotherapy for BP-I[15] as a treatment for BP-II depression. We compared IPSRT plus placebo to IPSRT plus quetiapine, an atypical antipsychotic medication that has established efficacy for BP-II depression.[16] Quetiapine therapy is associated with high levels of sedation and has documented metabolic risks.[17] We hypothesized that individuals who received IPSRT plus quetiapine would have better symptomatic outcomes than those assigned to IPSRT plus placebo but also more side effects. Broader goals of the study were to prospectively identify individuals who can be effectively managed with psychotherapy alone—a potential advantage for individuals who cannot tolerate medication side effects or who wish to

Clinical Points

- Little is known about the role of psychotherapy in managing bipolar II depression.
- Bipolar II depression treatment with psychotherapy plus medication results in more symptomatic improvement than psychotherapy alone but also more side effects.
- Psychotherapy alone is a reasonable treatment option for bipolar II depression, especially for those who prefer it and those for whom medication is relatively contraindicated.

avoid risks associated with medications. Thus, we sought to conduct exploratory moderator analyses to characterize subgroups who fared better with IPSRT plus placebo and those who needed medication to improve.

METHODS

This study (ClinicalTrials.gov identifier: NCT01133821) was conducted from 2010 to 2015 in an urban, academic medical center. All study procedures were approved by the University of Pittsburgh Institutional Review Board. Potential participants provided informed written consent after receiving a complete study description.

Study Design

This was a 20-week, randomized, double-blind, placebo-controlled, parallel-group study in adult outpatients with BP-II depression recruited from provider referrals, advertisements, and research registries. Participants were randomly assigned either to Interpersonal and Social Rhythm Therapy plus placebo (I+P) or Interpersonal and Social Rhythm Therapy plus quetiapine (I+Q).

Participants

Participants were men or women, 18–65 years of age, meeting *DSM-IV-TR*[18] criteria for BP-II, in a current major depressive episode, confirmed by Structured Clinical Interview for *DSM-IV* (SCID-I),[19] and scoring ≥ 15 on the 17-item Hamilton Depression Rating Scale (HDRS-17).[20]

Exclusion criteria were (1) any psychotic or organic mental disorder, BP-I, current alcohol or drug dependence, or borderline or antisocial personality disorder; (2) acute suicidal or homicidal ideation or requiring a higher level of psychiatric care; (3) nonfluent in English; (4) current participation individual psychotherapy; (5) prior lack of response to ≥ 12 weeks of IPSRT conducted by a trained therapist; (6) prior lack of response to ≥ 6 weeks of 300 mg of quetiapine; (7) current treatment with psychotropic medications; (8) pregnancy; or (9) active medical problem that better explained symptoms.

Psychotropic medications were prohibited except low doses of lorazepam (0.5–2 mg) for insomnia or agitation. Participants who met eligibility criteria but were on psychotropic medications at the time of informed consent were gradually tapered off medications and reevaluated to ensure that they still met eligibility criteria following 1 week off of all medications prior to randomization (Supplementary eTable 1, available at PSYCHIATRIST.COM).

Measures

Raters blind to treatment assignment conducted assessments at baseline and 8-, 12-, and 20-week follow-up except as indicated below. Diagnoses were confirmed with the SCID-I[19] and SCID-II.[21] Depressive symptoms were assessed weekly using the 17-item HDRS and the expanded 25-item version that includes reverse neurovegetative symptoms[22] and the Montgomery-Asberg Depression Rating Scale (MADRS).[23] Mania symptoms were rated weekly using the Young Mania Rating Scale (YMRS).[24] Interrater reliability, as measured by intraclass correlations, was 0.98, 0.99, and 0.98 for YMRS, HDRS-25, and HDRS-17, respectively.

Panic-Agoraphobic Spectrum Self-Report (PAS-SR)[25] measures lifetime panic-agoraphobic spectrum symptoms. Global illness severity was evaluated weekly using the Clinical Global Impressions Scale, Bipolar Version (CGI-BP), which includes separate clinician ratings for depression and mania on two 7-point Likert-type scales.[26] Functional Assessment Short Test (FAST)[27] is a 24-item measure of functioning for bipolar disorder with higher scores indicating more impairment. Composite Scale of Morningness (CSM),[28] a self-reported measure of diurnal preference for activity, ranges from 13 (extreme eveningness) to 55 (extreme morningness).

Multidimensional Assessment of Thymic States (MATHYS),[29] a self-administered visual analog scale, evaluates statelike emotional reactivity in the past week. Lower scores indicate inhibition/hyporeactivity; higher scores indicate excitation/hyperreactivity (range, 0–200).

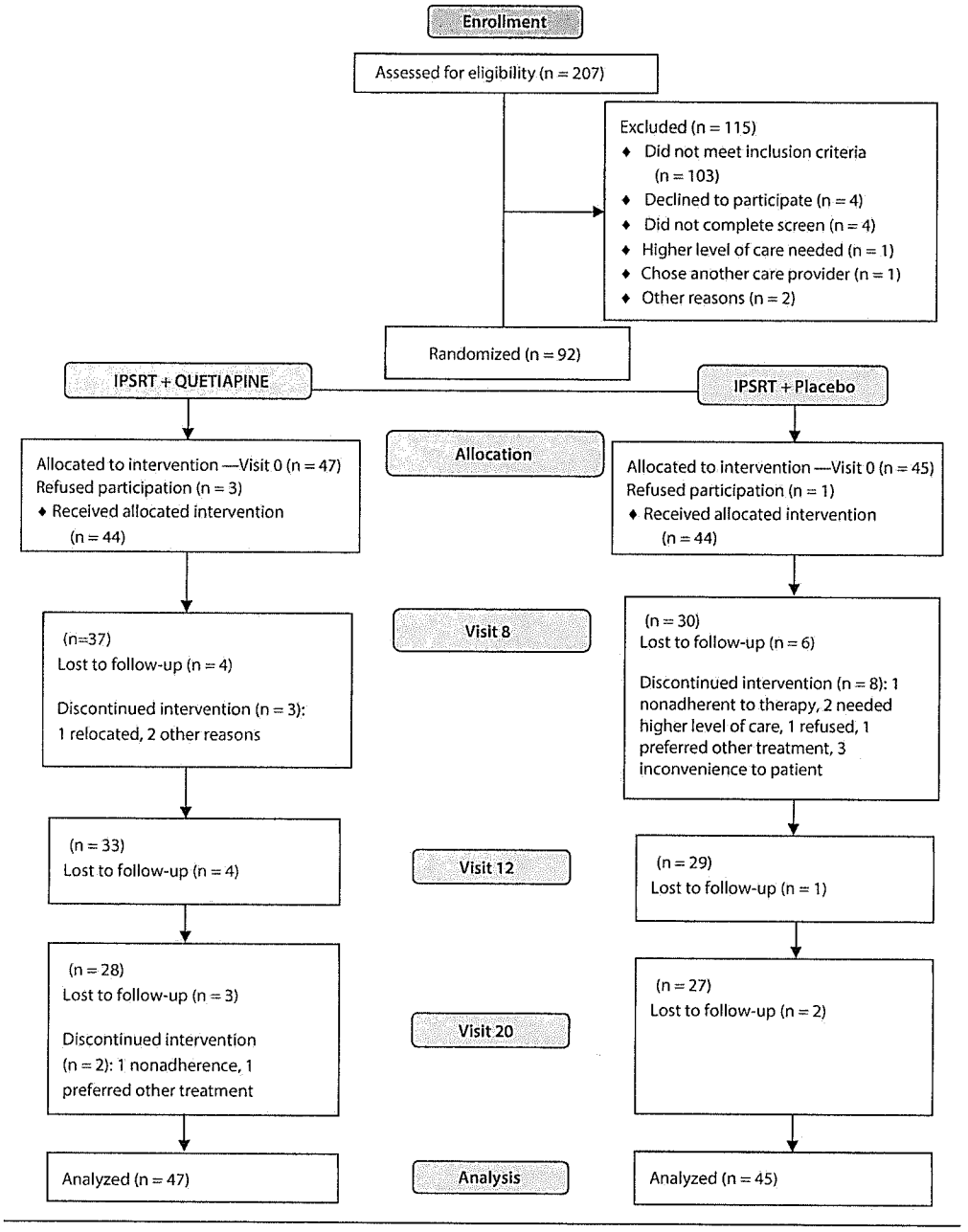
Treatment Response to Antidepressant Questionnaire (TRAQ)[30] is a semistructured interview designed to systematically collect information regarding previous antidepressant treatment, adequacy of trials, and nature of response. Individuals were coded as poor or good responders to antidepressants on the basis of prior treatment response.

Height was assessed at baseline and weight was measured at each treatment visit to calculate body mass index (BMI). Side effects were measured weekly with the Patient Rated Inventory of Side Effects (PRISE),[31] a standardized rating measure of somatic symptoms. An oversedation variable was created by combining 3 items from the PRISE (sleeping too much, fatigue, and decreased energy). Participants were asked prior to randomization whether they preferred treatment with psychotherapy alone, preferred psychotherapy and medication, or had no preference. For purposes of analyses, responses were dichotomized ("received preferred treatment" or "other").

Allocation

As the CONSORT diagram shows (Figure 1), 207 individuals were screened to yield 92 individuals eligible for randomization. Randomization was conducted by an

Figure 1. CONSORT Diagram



independent data manager not otherwise involved in study procedures. Assignment to I+Q (n = 47) or I+P (n = 45) was generated in random blocks. Because of the negative impact of co-occurring manic symptoms during depression[32] and comorbid borderline personality disorder on bipolar disorder outcomes,[33,34] randomization was stratified on baseline YMRS scores (≥ 10) and number of SCID-II borderline personality disorder traits endorsed (≥ 3).

Interventions

Each participant received 45-minute, individual, psychotherapy sessions from the same therapist. Participants were seen weekly until remission and then biweekly until week 20 and thus could receive up to 20 IPSRT sessions. Therapists (master's or doctoral level professionals with ≥ 3 years of clinical experience) administered IPSRT. Sessions were videorecorded or audiorecorded to monitor fidelity. All therapists participated in weekly supervision with expert supervisor feedback. Therapist adherence to IPSRT was assessed using the 22-item IPSRT Therapy Rating Scale.[35] Raters trained to maintain a criterion level of agreement within 1 point (ICC ≥ 0.80 for each scale item) rated a randomly selected subset (25%) of sessions to ensure fidelity. This instrument has been used in previous studies to evaluate the extent to which core components of IPSRT are present in sessions.

IPSRT, described in greater detail in the manual,[14] combines a focus on interpersonal relationships[36] with behavioral interventions to modify social rhythms. Patients develop more regular routines and sleep patterns to regulate underlying biologic abnormalities associated with BP-II, thereby reducing symptoms and improving outcomes. Patients completed a weekly self-report assessment, the Social Rhythm Metric (SRM),[37] to track and modify their social routines. IPSRT adapted for BP-II is described elsewhere.[7,38]

Quetiapine and placebo were dispensed in identically appearing capsules. Medication was flexibly dosed with a starting dose of 50 mg/d, increased weekly by 50 mg/d as tolerated to a maximum of 300 mg/d. Participants who could not tolerate 300 mg could remain in the study on the maximally tolerated dose. Participants who could not take any dosage of study medication were retained in the study on no medication but remained in their original allocation.

Analyses

Intent-to-treat analyses were conducted. Change over time on primary outcomes (HDRS, YMRS) and other continuous measures (MADRS, FAST) were evaluated using mixed effect models with maximum likelihood estimation and random intercept and slope. This approach creates a 2-level hierarchical model that nests time within individual.

To determine whether individual growth trajectories were nonlinear, higher-order polynomial models were tested, adding quadratic and cubic parameters to linear models. Goodness of fit of models were compared using 2 log-likelihood and Schwarz's Bayesian criterion indices. To test treatment effect on shapes of individual growth trajectories, treatment was examined as a time-invariant covariate to explore group differences in change over time. Treatment-by-time interactions were included in the models.

Potential moderators were selected a priori based on clinical relevance and evidence from the literature: age, gender, years of education, marital status, CSM score, number of hypomanic symptoms (baseline YMRS score), being on medication prior to entry, mood reactivity (MATHYS score), family history of bipolar disorders, prior treatment response to antidepressants (TRAQ), reverse neurovegetative symptoms (items 18 to 25 on HDRS-25), insomnia (items 4–6 on HDRS), lifetime anxiety (PAS-SR), and treatment preference.

To explore moderators of treatment outcome,[39] we constructed separate models that included treatment as an independent variable, one moderator, and their interaction. When the main effect of the moderator was significant but the interaction was not, the variable was considered a nonspecific predictor of outcome. When the interaction was significant, regardless of a significant main effect, the variable was considered a moderator. Continuous moderator variables were centered around the mean, and dichotomous variables were coded as −½, +½. Effect sizes for predictors and moderators were expressed as standardized regression coefficients. Moderator analyses were not corrected for multiple comparisons because they are hypothesis-generating.[39]

Statistical tests were performed at 2-sided 5% significance level ($\alpha = .05$). Analyses were conducted using SPSS, version 23 (IBM SPSS, Armonk, NY), and Stata, version 13 (StataCorp, LP, College Station, TX).

Table 1. Baseline Demographic and Clinical Variables

Variable	IPSRT+ Quetiapine (n=47)	IPSRT+ Placebo (n=45)	*P*
Gender, male, n (%)	15 (31.9)	19 (42.2)	.31
Age, mean±SD, y	30.9±10.3	33.9±11.2	.18
Ethnicity, Hispanic, n (%)	1 (2.1)	2 (4.4)	.53
Race, n (%)			
Caucasian	31 (66.0)	35 (77.8)	
African American	10 (21.3)	6 (13.3)	
Other	6 (12.7)	4 (8.9)	
Marital status, n (%)			.80
Never married	30 (63.8)	27 (60.0)	
Married/living as married	11 (23.4)	10 (22.2)	
Separated/divorced/widowed	6 (12.8)	8 (17.8)	
Education (highest level attained), n (%)			.11
High school diploma or less	4 (8.5)	9 (20.0)	
Some college or associate degree	26 (55.3)	22 (48.9)	
Bachelor's degree	11 (23.4)	13 (28.9)	
Graduate or professional degree	6 (12.8)	1 (2.2)	
Total income per year, n (%)			.19
<$30,000	27 (57.4)	21 (46.7)	
$30,000–$74,999	19 (40.4)	19 (42.2)	
≥$75,000	1 (2.1)	5 (11.1)	
Psychotropic medication prior to entering study, n (%)	6 (12.8)	11 (24.4)	.15
Duration of current depressive episode, median (IQR), wk	17 (8–114.5)	17 (8–88.5)	.48
Lifetime diagnosis of anxiety—*DSM-IV*, n (%)	31 (66.0)	29 (64.4)	.88
Current diagnosis of anxiety—*DSM-IV*, n (%)	28 (59.6)	26 (57.8)	.86
No. of lifetime episodes of depression, median	3	6	.07
No. of lifetime episodes of hypomania, median	6	12	.05
Hamilton Depression Rating Scale-17 score, mean±SD	19.6±3.9	21.0±4.6	.12
Hamilton Depression Rating Scale-25 score, mean±SD	24.7±4.9	26.0±5.4	.24
Young Mania Rating Scale score, mean±SD	6.2±3.5	6.2±3.4	.96
BMI, mean±SD	27.6±8.0	26.4±5.7	.53

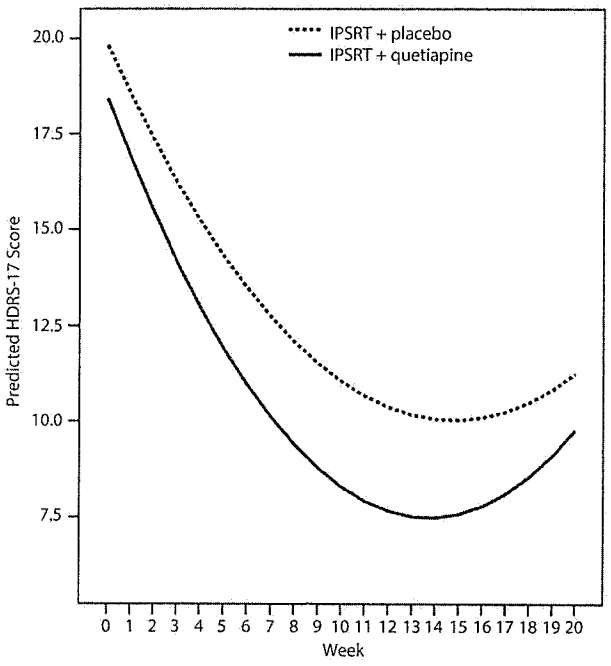
Abbreviations: BMI=body mass index, IPSRT=Interpersonal and Social Rhythm Therapy, IQR=interquartile range.

RESULTS

Baseline Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics of participants are provided in Table 1. Treatment groups differed only on number of prior hypomanic episodes: I+P had more (median=12) than I+Q (median=6). Although the finding was not statistically significant, almost twice as many participants in the I+P group (n=11; 24%) tapered off medication prior to

Figure 2. Estimated Change in Hamilton Depression Rating Scale-17 Item (HDRS-17) Scores Using Mixed-Effect Models[a]



[a]$F_{1,115.4} = 3.924$, $P = .048$. The curves represent the quadratic growth trajectories in the 2 groups over time.
Abbreviation: IPSRT = Interpersonal and Social Rhythm Therapy.

entry compared to I+Q (n = 6; 13%) (Supplementary eTable 1).

Outcomes by Treatment

Participants attended on average 11.6 (± 7.2) psychotherapy sessions over 20 weeks, without between-group differences ($t = 0.17$, $P = .865$). Mean quetiapine dosage was 172.3 ± 71.3 mg/d (range, 50–300 mg). Dropout rates were high (40%; Figure 1) but did not differ by treatment assignment or treatment preference (for both, $P > .05$). On primary outcomes, there were significant time effects for HDRS-17 ($F_{1,102.9} = 89.7$, $P < .001$) and YMRS ($F_{56.5} = 21.1$, $P < .001$), with a significant time-by-group interaction favoring I+Q (HDRS-17, $F_{1,115.4} = 3.924$, $P = .048$) for the quadratic term (see Figure 2) and YMRS ($F_{58.5} = 4.242$, $P = .044$) for the linear term. There were also significant time-by-group interactions favoring I+Q for MADRS ($F_{977.3} = 4.060$, $P = .044$) and CGI-Severity of Illness ($F_{1,054.4} = 8.197$, $P = .004$) scores. There were no group differences in FAST or SRM scores over time (for both, $P > .05$).

Both treatments yielded comparable response rates, defined as ≥ 50% reduction in HDRS-25 scores from baseline to endpoint: 67.4% (62/92) in the entire sample, with no significant between-group difference (60.0% [27/45] of I+P vs 74.5% [35/47] of I+Q; NS). Overall rates of remission (3 consecutive weeks with HDRS-25 ≤ 8 and YMRS ≤ 8) were 31.5% (29/92), with no between-group differences

Table 2. Participants Experiencing Self-Reported Side Effects on the Patient Rated Inventory of Side Effects

		IPSRT + Placebo (n = 38)		IPSRT + Quetiapine (n = 42)		χ^2 Test
		n	%	n	%	*P* Value[a]
Diarrhea	no	21	55.3	22	52.4	.796
	yes	17	44.7	20	47.6	
Constipation	no	24	63.2	18	42.9	.069
	yes	14	36.8	24	57.1	
Dry mouth	no	16	42.1	9	21.4	**.046**
	yes	22	57.9	33	78.6	
Nausea/vomiting	no	16	42.1	18	42.9	.946
	yes	22	57.9	24	57.1	
Palpitations	no	20	52.6	20	47.6	.654
	yes	18	47.4	22	52.4	
Dizziness on standing	no	17	44.7	17	40.5	.700
	yes	21	55.3	25	59.5	
Chest pain	no	23	60.5	28	66.7	.568
	yes	15	39.5	14	33.3	
Rash	no	28	73.7	36	85.7	.179
	yes	10	26.3	6	14.3	
Increased perspiration	no	23	60.5	28	66.7	.568
	yes	15	39.5	14	33.3	
Itching	no	20	52.6	24	57.1	.685
	yes	18	47.4	18	42.9	
Dry skin	no	15	39.5	13	31.0	.425
	yes	23	60.5	29	69.0	
Headache	no	5	13.2	6	14.3	.884
	yes	33	86.8	36	85.7	
Tremors	no	27	71.1	30	71.4	.970
	yes	11	28.9	12	28.6	
Poor coordination	no	21	55.3	16	38.1	.124
	yes	17	44.7	26	61.9	
Dizziness	no	19	50.0	16	38.1	.284
	yes	19	50.0	26	61.9	
Blurred vision	no	24	63.2	22	52.4	.330
	yes	14	36.8	20	47.6	
Ringing in ears	no	28	73.7	24	57.1	.121
	yes	10	26.3	18	42.9	
Difficulty urinating	no	31	81.6	36	85.7	.617
	yes	7	18.4	6	14.3	
Painful urination	no	36	94.7	35	83.3	.107
	yes	2	5.3	7	16.7	
Frequent urination	no	22	57.9	21	50.0	.479
	yes	16	42.1	21	50.0	
Menstrual irregularity	no	31	81.6	30	71.4	.287
	yes	7	18.4	12	28.6	
Difficulty sleeping	no	5	13.2	9	21.4	.331
	yes	33	86.8	33	78.6	
Sleeping too much	no	9	23.7	4	9.5	.086
	yes	29	76.3	38	90.5	
Loss of sexual desire	no	15	39.5	14	33.3	.568
	yes	23	60.5	28	66.7	
Trouble achieving orgasm	no	23	60.5	21	50.0	.345
	yes	15	39.5	21	50.0	
Trouble with erections	no	32	84.2	35	83.3	.915
	yes	6	15.8	7	16.7	
Anxiety	no	2	5.3	6	14.3	.179
	yes	36	94.7	36	85.7	
Poor concentration	no	4	10.5	6	14.3	.612
	yes	34	89.5	36	85.7	
General malaise	no	12	31.6	12	28.6	.769
	yes	26	68.4	30	71.4	
Restlessness	no	2	5.3	10	23.8	**.020**
	yes	36	94.7	32	76.2	
Fatigue	no	3	7.9	5	11.9	.550
	yes	35	92.1	37	88.1	
Decreased energy	no	3	7.9	3	7.1	.899
	yes	35	92.1	39	92.9	
Other (specify)	no	27	71.1	27	64.3	.519
	yes	11	28.9	15	35.7	

[a]Boldface indicates statistical significance.
Abbreviation: IPSRT = Interpersonal and Social Rhythm Therapy.

Table 3. Effect Sizes (outcomes) for Statistically Significant Predictors and Moderators[a]

Variable	Nonspecific Predictor	Moderator Favoring IPSRT + Quetiapine	Moderator Favoring IPSRT + Placebo	Comment
Young Mania Rating Scale (YMRS)	0.11 (change in Functional Assessment Short Test)		−0.08 (treatment response; ≥ 50% reduction in HDRS-25 scores from baseline to endpoint)	Higher YMRS score predicted more rapid improvement in functioning ($F = 6.037$, $P = .016$) and was associated with increased likelihood of response in those assigned to IPSRT + placebo (OR = 0.872, $P = .048$)
Multidimensional Assessment of Thymic States	−0.01 (change in HDRS-25)	−0.04 (change in Functional Assessment Short Test)		Hyperreactivity predicted faster improvement in depression ($F = 5.243$, $P = .025$) and more rapid improvement in functioning in those assigned to IPSRT + quetiapine ($F = 5.947$, $P = .017$)
Reverse neurovegetative symptoms	0.11 (change in HDRS-25)			Fewer atypical depression symptoms was associated with faster improvement in depression ($F = 7.087$, $P = .009$)
Panic-Agoraphobic Spectrum Self-Report (PAS-SR)	0.02 (change in HDRS-25)			Lower PAS-SR scores were associated with more rapid improvement in depression ($F = 10.738$, $P = .002$)
Composite Scale of Morningness	0.57 (change in BMI)	−0.06 (change in HDRS-25)		Eveningness showed a trend toward predicting greater BMI reductions ($F = 3.572$, $P = .060$) and morningness was associated with faster improvement in depression in those assigned to IPSRT + quetiapine ($F = 7.219$, $P = .009$)
Treatment preference	0.49 (treatment response; ≥ 50% reduction in HDRS-25 scores from baseline to endpoint)			Receiving preferred treatment was associated with increased likelihood of response (OR = 4.48, $P = .026$)

[a]Effect sizes are expressed as standardized regression coefficients. Effect sizes for moderators are derived from the variable-by-treatment interaction term and those for predictors from the main effect of the variable.
Abbreviations: BMI = body mass index, HDRS-25 = Hamilton Depression Rating Scale-25 Item, IPSRT = Interpersonal and Social Rhythm Therapy, OR = odds ratio.

(28.9% [13/45] of I+P vs 34.0% [16/47] of I+Q; NS). In the quetiapine group, mean final dose (mg) was 209.0 ± 75.1 in remitters (n = 16) versus 143.15 ± 96.9 nonremitters (n = 31) ($t = 2.37$, $P < .05$). Significantly more individuals in I+P used at least one dose of lorazepam: 60% (27/45) in I+P versus 34% (16/47) in I+Q ($\chi^2 = 6.22$, $P = .013$). Only 7% (6/92) of participants experienced a single YMRS score ≥ 15 over the course of the study, and this did not differ by group. No one experienced an episode of mania. Although study medication was administered double-blind, participants receiving quetiapine correctly guessed treatment assignment (at either week 8 or 20; last available guess) numerically more often than those assigned to I+P (91% [29/32] vs 75% [21/28]), but this difference was not statistically significant (Fisher exact test, $P = .10$).

Those assigned to I+Q experienced a modest estimated linear increase in BMI over time from 28.1 to 28.6 kg/m^2, in contrast to a slight decline in BMI among those assigned to I+P from 26.8 to 26.7 kg/m^2 ($F_{67.96} = 6.671$, $P = .012$). Early weight gain (> 5% in first month) occurred in 5% (2/44) of those in I+Q and none in I+P (NS). In a subset for whom PRISE information was available (n = 80), those assigned to I+Q reported at least once during the study significantly higher rates of dry mouth (79% vs 58%; $\chi^2 = 4.0$, $P = .046$) and a trend toward higher rates of oversedation (100% vs 92%; $\chi^2 = 3.4$, $P = .063$) versus I+P. By contrast, complaints of restlessness were significantly higher in the I+P group (95% vs 76%; $\chi^2 = 5.4$, $P = .02$). See Table 2 and Supplementary eFigure 1.

Moderators of Treatment Outcomes

Baseline YMRS scores moderated treatment response, with those experiencing > 9 hypomanic symptoms less likely to respond to I+Q (OR = 0.872, 95% CI = 0.760–0.999, $P = .048$) than to I+P (see Supplementary eFigure 2). MATHYS total score was a moderator of functional outcomes (change in FAST scores), with those scoring above the mean (more hyperreactivity) more likely to improve with I+Q ($F_{94.1} = 5.947$, $P = .017$) than I+P. CSM scores moderated outcomes such that higher scores (more morningness) were associated with greater improvement in HDRS-25 scores in those randomized to I+Q ($F_{69.2} = 7.219$, $P = .009$). See Table 3 for a summary of effect sizes for significant moderators.

Family history of bipolar disorder, prior treatment response to antidepressant, reverse neurovegetative symptoms, insomnia, PAS-SR scores, and treatment preference were not moderators of outcomes.

Predictors of Treatment Outcomes

Total MATHYS score was a nonspecific predictor of outcome, with those scoring above the mean (hyperreactivity) having greater improvement on HDRS-25 than those scoring below the mean ($F_{71.8} = 5.243$, $P = .025$).

Fewer reverse neurovegetative symptoms ($F_{110.9} = 7.087$, $P = .009$) and low PAS-SR scores ($F_{70.2} = 10.738$, $P = .002$) predicted more rapid improvement on the HDRS-25. Treatment preference was a significant predictor of response, such that individuals randomized to their preferred treatment were 4.5 times more likely to respond, regardless of assignment (OR = 4.48, 95% CI = 1.20–16.77, $P = .026$). YMRS scores were positive predictors of FAST scores, with higher scores predicting greater change in functioning ($F_{100.5} = 6.037$, $P = .016$).

Family history of bipolar disorder, prior treatment response to antidepressant, insomnia, and CSM scores were not predictors of outcomes.

DISCUSSION

Treatment with IPSRT and quetiapine yielded better symptomatic outcomes; however, I+Q was also associated with more side effects, including a statistically significant increased risk for weight gain (increased BMI). Absolute weight gain was small, and only 5% of the I+Q group met criteria for early weight gain (>5% in first month), a strong predictor of subsequent weight gain.[40] Given the growing global burden of obesity[41] and likelihood that obesity negatively affects the course of bipolar disorder,[42] this modest difference constitutes a nontrivial treatment consideration. Because of the chronicity of BP-II and need for maintenance treatment, a relatively small increase in BMI observed over 20 weeks could be even greater if exposure to quetiapine were to continue over years or even decades. In other studies, more than 50% of quetiapine-exposed patients gained significant weight over a year of treatment.[43,44]

All participants improved on primary symptom measures (HDRS, YMRS), including those who received IPSRT alone. Sixty percent of those assigned to I+P responded to treatment, rates comparable to those seen with pharmacotherapy alone.[16] This suggests that, for those who do not wish to incur the risks of weight gain, dry mouth, or sedation, IPSRT alone is a viable option. Interestingly, those with higher YMRS scores (>9) at baseline did better with I+P than I+Q. Within the very truncated distribution observed in this trial (by definition, no episodes of mania), higher YMRS scores may be a proxy for increased energy, allowing individuals with higher energy to take steps required to make optimal use of psychotherapy. This result should be interpreted with caution, however, because only 8 individuals in the I+P group and 10 individuals in the I+Q group had YMRS scores >9. More I+P participants complained of restlessness on the PRISE, suggesting that addition of quetiapine mitigated intolerable agitation/activation.

Those with low CSM scores (below the median value of 30) fared better with IPSRT plus quetiapine, suggesting that morningness traits may enable those who are somewhat phase advanced to better tolerate quetiapine-induced sedation. Individuals whose clinical presentation was characterized by hypersomnia, anergia, hyperphagia, hyporeactivity, and high lifetime anxiety symptoms improved more slowly, regardless of intervention received, suggesting that these individuals may require longer or different courses of treatment.

Perhaps informed by prior treatment experiences or self-knowledge, treatment preference was a potent global predictor of response, showing that those who got the treatment they preferred did better and suggesting that patient preference—including the option of psychotherapy monotherapy—should be considered when managing BP-II depression.

The mean dose of quetiapine in this study (172 mg) was lower than the 300–600 mg used in trials with forced titration schedules,[16] raising the intriguing possibility that combining medication with a bipolar-specific psychotherapy may enable individuals to be managed with lower-than-usual doses of medications, thus potentially mitigating some side effects. This hypothesis, although not formally tested in this trial, is perhaps supported by the fact that weight gain, though present, was somewhat lower than in other quetiapine studies that used higher doses.[43,44] An alternate hypothesis is that individuals with BP-II may require lower doses of quetiapine than those with BP-I.

Because maintenance treatment is recommended for BP-II,[45] evaluation of both interventions needs to be considered in light of implications for long-term follow-up. Whether psychotherapy alone will suffice as a maintenance treatment for BP-II is unknown. Risk of metabolic dysregulation in bipolar disorder[46] and burdens of long-term exposure to medications like quetiapine,[47,48] however, are well documented. Thus, low-side-effect treatment options like IPSRT monotherapy are appealing, but longer term research is needed before it can be recommended.

Limitations of the current study include absence of an inactive psychotherapy comparator, high dropouts, and overall poor remission rates. Medication withdrawal phenomena may have disadvantaged a subset of participants. Effect sizes for moderators and predictors were small and uncorrected for multiple comparisons, suggesting that although findings were statistically significant, they require confirmation in a larger trial. Power was limited for some comparisons, potentially leading to type II errors. Correct guessing of treatment assignment indicates failure of blinding for participants, although raters remained blinded. Our sample was predominantly white and relatively well educated, which may limit generalizability of findings to other groups.

In conclusion, symptomatic benefits were greater when patients were treated with IPSRT plus quetiapine, but this additional improvement came with a risk of more side effects. A subset of patients did well with IPSRT plus placebo, especially those who preferred this modality. Although it is not typically offered to those with bipolar II disorder, IPSRT alone appears to be a reasonable treatment option, especially for those who prefer it, individuals motivated to implement psychotherapeutic recommendations, and those for whom medication is relatively contraindicated. Future studies should look at combined moderators of outcomes to develop personalized treatment algorithms for bipolar II disorder.

Submitted: June 16, 2016; accepted November 28, 2016.

Published online: July 11, 2017.

Potential conflicts of interest: **Dr Swartz** receives royalties from UpToDate. **Dr Frank** receives royalties from the American Psychological Association and Guilford Press; she and her spouse serve on an advisory board to Servier International; she and her spouse have equity in Minerva Neuroscience, HealthRhythms, and Psychiatric Assessments; and her spouse has equity in Aliphcom and Minerva Neuroscience and receives royalties from the Pittsburgh Sleep Quality Index. During the past 3 years, **Dr Thase** has been a consultant to Alkermes, Allergan (including Actavis, Forest, and Naurex), AstraZeneca, Avenir, Aventis, Bristol-Myers Squibb, Cerecor, Eli Lilly, Gerson Lehman Group, Guidepoint Global, Janssen (includes Johnson & Johnson), H. Lundbeck A/S, MedAvante, Merck, Neuronetics, Novartis, Otsuka, Nestle (includes PamLab), Pfizer, Roche, Shire US, Sunovion, Takeda, and Teva. During the same time frame, he has received research grants from Agency for Healthcare Research and Quality, Alkermes, AstraZeneca, Avenir, Eli Lilly, Forest, GlaxoSmithKline, Janssen (Johnson & Johnson), the National Institute of Mental Health, Otsuka, Pharmaneuroboost, Roche, and Takeda. **Drs Rucci, Wallace,** and **Carretta** and **Ms Celedonia** report no financial relationships with commercial interests.

Funding/support: This study was funded by the National Institute of Mental Health (NIMH) R01 MH084831 (Dr Swartz, principal investigator).

Role of the sponsor: NIMH had no role in data collection, data management, data analysis, or interpretation of data or in the preparation, review, or approval of the manuscript. NIMH approved the study design and provided oversight of the conduct of the study (accrual of subjects, yearly monitoring of study progress).

Previous presentation: Presented at the American Society of Clinical Psychopharmacology Annual Meeting in Phoenix, Arizona, May 30–June 3, 2016, and at the ISBD Annual Meeting in Amsterdam, The Netherlands, July 13–16, 2016.

Acknowledgments: The authors thank the individuals who participated in this research project and the clinicians and staff who contributed to the conduct of this trial.

Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Psychotherapy Alone and Combined With Medication as Treatments for Bipolar II Depression: A Randomized Controlled Trial

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DOI Number: 10.4088/JCP.16m11027

List of Supplementary Material for the article

1. eTable 1 Psychotropic Medications Discontinued Prior to Starting Trial
2. eFigure 1 Estimated Change in Body Mass Index (BMI) Values Using Mixed-Effect Models
3. eFigure 2 Baseline Young Mania Rating Scale (YMRS) as Moderator of Treatment Response

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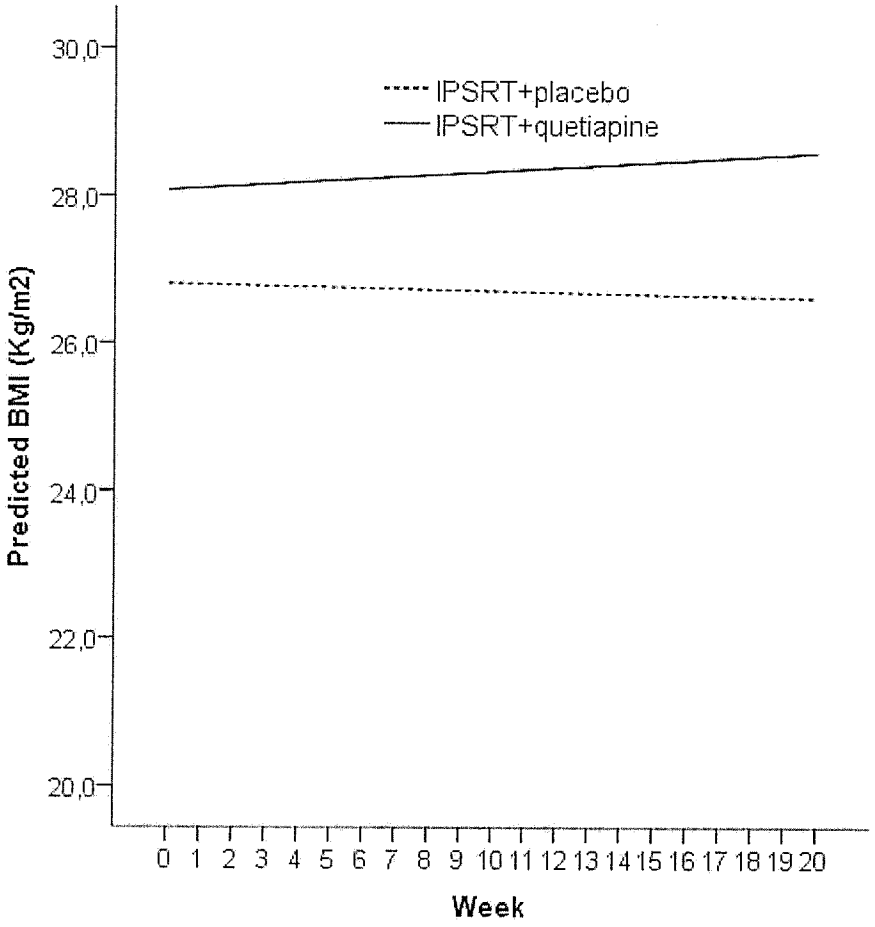
Supplementary eTable 1. Psychotropic Medications Discontinued Prior to Starting Trial

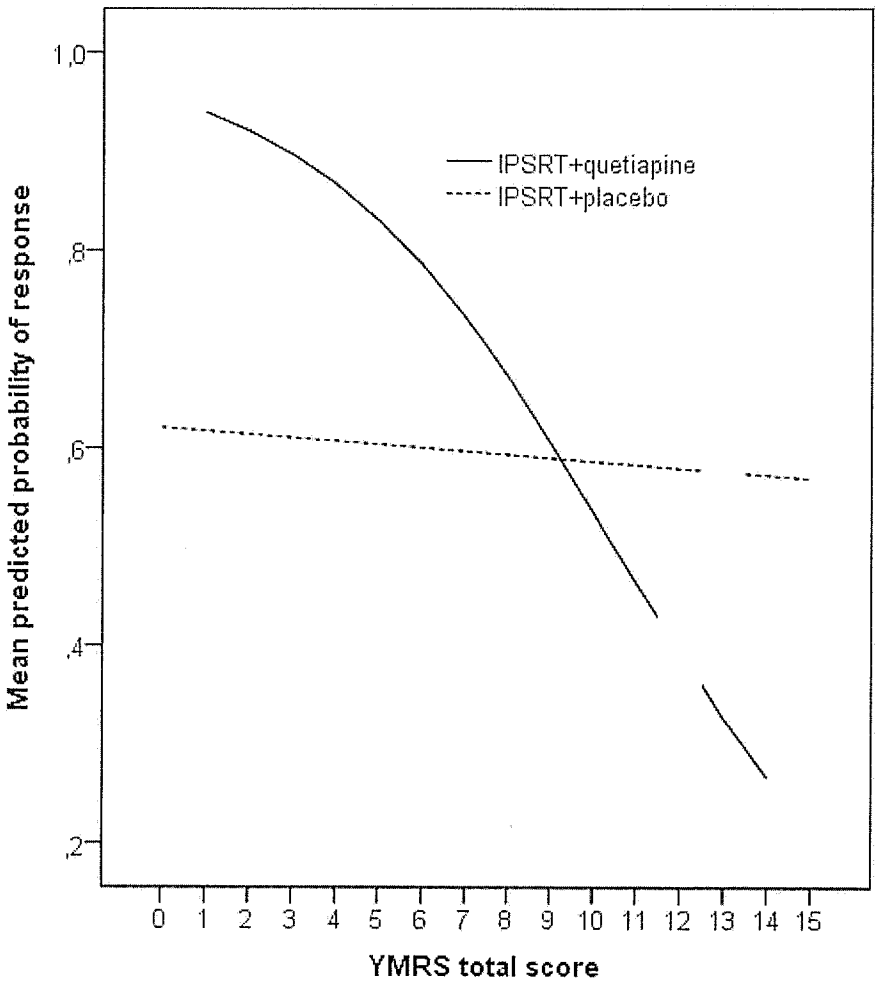
Randomization Group	Participant	Medication	Dose
IPSRT +PLACEBO	1	Trazodone	200 mg qhs
		Bupropion	300 mg daily
		Sertraline	150 mg daily
	2	Sertraline	100 mg daily
	3	Aripiprazole	5 mg daily
		Bupropion	150 mg daily
		Desvenlafaxine	100 mg daily
	4	Citalopram	20 mg daily
		Valproate	1000 mg daily
	5	Eszopiclone	1 mg qhs prn
		Temazepam	1 mg qhs prn
		Vilazodone	40 mg qhs
	6	Mixed amphetamine salts	5 mg daily
		Lithium carbonate	900 mg daily
		Trazodone	50 mg qhs prn
	7	Duloxetine	30 mg daily
	8	Mixed amphetamine salts	20 mg daily
	9	Bupropion	100 mg daily
		Alprazolam	0.25 mg daily prn
	10	Alprazolam	0.25 mg daily prn
	11	Aripiprazole	1 mg daily
		Citalopram	20 mg daily
IPSRT + QUETIAPINE	13	Escitalopram	10 mg daily
	14	Sertraline	50 mg daily
	15	Citalopram	30 mg daily
	16	Duloxetine	60 mg daily
	17	Sertraline	200 mg daily
	18	Zolpidem	2.5 mg qhs prn

Supplementary eFigure 1. Estimated change in Body Mass Index (BMI) values Using Mixed-Effect Models (a)



(a) (F=6.671, df=67.96; p=.012) The curves represent an estimated linear model

Supplementary eFigure 2. Baseline Young Mania Rating Scale (YMRS) as Moderator of Treatment Response (a)



(a) Curves show decreased predicted probability of response to IPSRT plus quetiapine compared to IPSRT plus placebo with > 9 hypomanic symptoms (OR=0.872, 95% CI= 0.760-0.999, p=.048)