A randomized pilot study of psychotherapy and quetiapine for the acute treatment of bipolar II depression

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Abstract

Objectives—The differential roles of psychotherapy and pharmacotherapy in the management of bipolar (BP) II depression are unknown. As a first step toward exploring this issue, we conducted a pilot study to evaluate the feasibility and acceptability of comparing a bipolar-specific psychotherapy [Interpersonal and Social Rhythm Therapy (IPSRT)] to quetiapine as treatments for BP-II depression.

Methods—Unmedicated individuals (n = 25) meeting DSM-IV criteria for BP-II disorder, currently depressed, were randomly assigned to weekly sessions of IPSRT (n = 14) or quetiapine (n = 11), flexibly dosed from 25–300 mg. Participants were assessed with weekly measures of mood and followed for 12 weeks. Treatment preference was queried prior to randomization.

Results—Using mixed effects models, both groups showed significant declines in the 25-item Hamilton Rating Scale for Depression [$F(1,21) = 44$, $p < 0.0001$] and Young Mania Rating Scale [$F(1,21) = 20$, $p = 0.0002$] scores over time but no group × time interactions. Dropout rates were 21% (n = 3) and 27% (n = 3) in the IPSRT and quetiapine groups, respectively. Overall response rates (defined as ≥ 50% reduction in depression scores without an increase in mania scores) were 29% (n = 4) in the IPSRT group and 27% (n = 3) in the quetiapine group. Measures of treatment satisfaction were high in both groups. Treatment preference was not associated with outcomes.

Conclusions—Outcomes in participants with BP-II depression assigned to IPSRT monotherapy or quetiapine did not differ over 12 weeks in this small study. Follow-up trials should examine characteristics that predict differential response to psychotherapy and pharmacotherapy.

Keywords

bipolar II disorder; pharmacotherapy; psychotherapy; treatment

Bipolar (BP) II disorder is a highly recurrent disorder (1) associated with elevated levels of psychosocial impairment (2, 3), disability (4), comorbidity (3, 5), and suicidal ideation/behaviors (6, 7) . Despite the significant suffering associated with BP-II disorder, relatively little is known about how best to treat this illness (8). Uncertainty about management of BP-II is complicated by the fact that depression is the dominant pole of BP-II disorder (1), a phase of the disorder for which we have relatively few effective treatments (9, 10).

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Despite the large side effect burden associated with medications used to treat BP disorders (8, 11) and the large lacunae in the evidence base with respect to their efficacy (12), alternatives to pharmacotherapy are rarely considered in mainstream treatment algorithms (8, 13). Psychotherapy, which arguably has no side effects (14), may play an important role in the management of BP-II disorder as many individuals suffering from the illness struggle with issues that lend themselves to psychosocial remediation. For instance, recognition and treatment of BP-II disorder often lags years behind initial manifestation of symptoms (15), a problem which is associated with a chronic course of illness (1) and subsequent erosion in psychosocial functioning (2, 4). Further, individuals with BP-II disorder typically have difficulty distinguishing among rapid mood shifts and subtle mood states (i.e., hypomania) that characterize BP-II (16), and yet ability to recognize mood symptoms likely constitutes the first step toward effective disease management. Bipolar-specific psychotherapies can provide patients with strategies for understanding their illness, managing symptoms, and enhancing psychosocial functioning (17, 18).

Although use of psychotherapy alone as an alternative to pharmacotherapy is likely contraindicated in BP-I disorder, it is not unreasonable to consider this approach in BP-II disorder where individuals are at low risk of experiencing fully syndromal manic episodes or psychosis. Despite the compelling argument to be made for its inclusion in the therapeutic armamentarium for BP-II disorder, the literature on psychotherapy for the treatment of BP-II disorder is sparse. When used in combination with mood stabilizers, bipolar-specific psychotherapies have been shown to shorten time to recovery in patients suffering from BP disorders, including a subset of individuals diagnosed with BP-II disorder (19). A small group of individuals meeting criteria for BP-II disorder who received group psychoeducation in addition to pharmacotherapy had better long term (five year) outcomes than patients receiving a control psychosocial intervention (20). We have previously demonstrated feasibility of treating patients meeting criteria for BP-II depression with psychotherapy alone (21). There are no comparative trials of psychotherapy and pharmacotherapy.

Interpersonal and Social Rhythm Therapy (IPSRT) is an evidence-based psychotherapy for bipolar disorder (22). In randomized clinical trials where IPSRT was used in combination with medication, IPSRT has been shown to reduce time to recovery from an episode of depression (19), decrease the likelihood of mood episode recurrence (23), and improve psychosocial and occupational functioning (24, 25). We have modified IPSRT for use as monotherapy with individuals who have BP-II disorder (16, 21).

In order to advance understanding of the roles of psychotherapy and pharmacotherapy in the management of BP-II depression, we conducted a small randomized trial of IPSRT versus quetiapine, a second generation antipsychotic that has demonstrated efficacy as treatment for BP-II depression (26–28). The primary goal was to evaluate the feasibility and acceptability of this approach. A secondary goal was to examine symptomatic and functional outcomes over a 12-week period in patients assigned to the two treatment conditions.

Methods

Study design

All study procedures were reviewed and approved by the Biomedical Institutional Review Board of the University of Pittsburgh, Pittsburgh, PA, USA. Potential participants provided informed written consent after receiving a complete description of the study. Participants were recruited by word of mouth from other investigators and clinicians.

Seventy-six potential participants consented to screening for inclusion in the protocol during the study period (December 9, 2006 through July 1, 2010). A total of 25 participants were deemed eligible for inclusion in the protocol based on the following criteria: (i) age 18 to 65 years; (ii) lifetime diagnosis of BP-II disorder, currently depressed; (iii) Hamilton Rating Scale for Depression (HRSD-17) (29) score ≥ 15; (iv) Young Mania Rating Scale (YMRS) (30) score ≤ 10; and (v) willingness to accept randomization to medication or psychotherapy. Individuals were excluded from the study if they met any of the following criteria: (i) concurrent treatment with psychoactive medications; (ii) diagnosis of substance abuse or dependence within the prior six months; (iii) diagnosis of borderline or antisocial personality disorder; and (iv) unstable medical condition that could produce symptoms that would confound accurate assessment of mood symptoms (e.g., untreated thyroid disease). Six of the 25 eligible participants were receiving psychotropic medication(s) prior to study entry. They were tapered off of medication and reassessed to determine continued eligibility. One week off of psychotropic medications, all six participants continued to meet eligibility criteria (five assigned to IPSRT and one assigned to quetiapine; this difference was not statistically significant, p = 0.18).

Demographic data and psychiatric treatment history were recorded on standardized research forms. Lifetime and current psychiatric diagnoses were assigned using the Structured Clinical Interview for DSM-IV–clinician version [SCID-I (31) and SCID-II (32)]. Depressive symptoms were assessed using the 17-item HRSD, the expanded 25-item version of the HRSD that includes reverse neurovegetative symptoms (33), and the Montgomery-Åsberg Depression Rating Scale (MADRS) (34). Mania symptoms were rated using the YMRS. Global functioning was evaluated 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 (35). Anxiety symptoms were assessed using the self-report Beck Anxiety Inventory (BAI) (36). Research assessments were conducted by raters who were not involved in the participants' treatment. Inter-rater reliability as measured by intraclass correlations (ICC) were excellent: ICC = 0.99, 0.99, and 0.98 for YMRS, HRSD-25, and HRSD-17, respectively. Satisfaction with the intervention was assessed at visit 12 with the Client Satisfaction Questionnaire (CSQ) (37) which yields scores ranging from 8 to 32 with higher scores indicating greater levels of satisfaction. Weight was measured at each treatment visit. Participants were asked prior to randomization whether they preferred treatment with psychotherapy or medication.

Participants were randomly assigned using a permuted block strategy (38) to either IPSRT (n = 14) or quetiapine (n = 11). The trial ended prior to completing expected enrollment (n = 30), and therefore the cell sizes were uneven (truncation of randomization occurred in the middle of a block).

IPSRT—Those assigned to IPSRT received weekly, 45-minute, individual psychotherapy sessions. IPSRT is described in greater detail in the manual (22). Briefly, IPSRT combines a focus on interpersonal relationships (39) with psychoeducation and a behavioral intervention designed to modify social rhythms. Psychoeducation in IPSRT focuses on understanding BP-II disorder with a focus on identification of hypomania and mixed or dysphoric mood states. The social rhythm component of IPSRT postulates that disordered circadian biology contributes to the development and maintenance of psychiatric symptoms and that helping patients to develop more regular routines and social patterns can help regulate underlying circadian abnormalities, thereby reducing symptoms and improving outcomes. Patients complete a weekly self-report assessment, the Social Rhythm Metric (SRM) (40), to track the regularity of their social routines. Patients are encouraged to develop more regular sleep and activity patterns and modify their social interactions in order to promote mood stability. Special issues arising in the use of IPSRT for BP-II disorder are described elsewhere (16).

IPSRT sessions were delivered by three master's level therapists, and all therapy sessions were audio- or video- recorded for fidelity monitoring.

Quetiapine—Those assigned to quetiapine met weekly with a psychiatrist for medication management. Quetiapine was flexibly dosed with a starting dose of 50 mg per day, increased weekly by 50 mg/day as tolerated to a maximum of 300 mg/day.

Participants in either condition who experienced sleep disturbances that could not be managed with study treatments alone could receive low doses of lorazepam at any point during the study at the discretion of the treating psychiatrist.

Data analysis

For baseline demographic and clinical characteristics, Wilcoxon tests and Fisher Exact tests were used to compare continuous and categorical variables, respectively. Longitudinal data were analyzed using an intent-to-treat approach with mixed effect models with fixed terms including group and time, and group by time interaction. Time was treated as a continuous variable for those variables measured frequently and as a repeated factor for those variables taken only at baseline and 12 week follow-ups. Individual variabilities were taken into account by including random intercept and random slope for linear mixed models and participant as a random term for repeated measures mixed models.

Results

There were no significant differences in baseline demographic and clinical characteristics of the two groups (Table 1). When asked about treatment preference prior to randomization, 40% (10/25) expressed a preference for medication, 40% (10/25) a preference for psychotherapy, and 20% (5/25) no preference. Two participants met all study eligibility requirements but did not come to a single treatment session (one in each treatment condition). In the IPSRT condition, fifteen percent (n = 2) dropped out after having had at least one study visit (mean number of visits prior to drop out = 3.5 ± 2.1; range: 2–5). In the quetiapine condition, 20% (n = 2) dropped out after having had at least one study visit (mean number of visits prior to drop out, 4 ± 1.4; range: 3–5). Mean number of IPSRT sessions over 12 weeks was 8.5 (± 2.8). Mean number of medication management sessions attended by those assigned to quetiapine was 8.0 (± 2.6). Mean dose of quetiapine at week 12 (n = 8) was 243.8 mg (± 67.8; range: 25–300). Twenty-one percent (n = 3) of the IPSRT group received adjunctive lorazepam (mean dose 1.3 ± 0.6 mg) versus 0% assigned to quetiapine, but this was not statistically significant.

As shown in Figures 1 and 2, there were significant improvements over time in both depressive and hypomanic symptoms in both treatment conditions. Mixed-effects analyses showed significant time effects for symptoms as measured by HRSD-25 [$F(1,21) = 44$, $p < 0.0001$], HRSD-17 [$F(1,21) = 49$, $p < 0.0001$], YMRS [$F(1,21) = 20$, $p = 0.0002$], BAI [$F(1,20) = 15$, $p = 0.001$], and MADRS [$F(1,23) = 35$, $p < 0.0001$], and in overall illness severity as measured by CGI-severity [$F(1,20) = 31$, $p < 0.0001$]. Weight also increased significantly over time in both groups [$F(1,20) = 5.9$, $p = 0.03$]. There was no significant time by group interaction on any variable. Treatment preference was initially included as a covariate in these models and found to be significantly correlated only with BAI scores [$F(2,105) = 3.18$, $p = 0.05$] with individuals who preferred medication having significantly lower BAI scores relative to those preferring psychotherapy [$t(105) = -2.49$, $p = 0.015$]. There was no significant interaction with time, however. Considering the relatively small sample size, treatment preference was therefore dropped as a covariate in subsequent analyses.

Using categorical outcomes, 29% (n = 4) of the sample responded to IPSRT monotherapy and 27% (n = 3) responded to quetiapine (defined as ≥ 50% reduction in HRSD-25 scores and YMRS ≤10) by visit 12. There were no significant differences in response rates between groups. CSQ scores at week 12 were 26.6 ± 3.7 and 27.1 ± 3.8 in the IPSRT (n = 11) and quetiapine (n = 8) completer groups, respectively, with no differences between groups.

Discussion

In this study, we found no differences in outcomes among participants with BP-II depression assigned to either medication or psychotherapy over 12 weeks. Treatment satisfaction was high in both conditions and dropout rates were relatively low compared to other BP-II clinical trials (26). Individuals who preferred psychotherapy to medication had higher anxiety scores, but this is not surprising given the heightened sensitivity of those with anxiety to somatic experiences (41), including medication side effects. Nevertheless, the sample was evenly divided with respect to treatment preference (40% expressed a preference for medication and 40% a preference for psychotherapy prior to randomization), and treatment preference was not associated with treatment outcomes. Both treatment groups experienced significant reductions in mood and anxiety symptoms over time, but there were no group × time interactions. Weight gain was seen in the entire sample, independent of treatment assignment. This underscores the importance of attending to latent metabolic risk factors in individuals with BP disorders (42), including those with BP-II disorder.

The small sample size limits conclusions that can be drawn about efficacy from this trial (43). Observed response rates across groups are lower than those seen in prior trials of quetiapine for BP-II depression (26) which may reflect either real differences in the populations or an artifact of a small trial. Nevertheless, absence of differences between the two groups on all outcome measures and the high degree of acceptability across groups (as measured by high scores on the CSQ and 25% dropout rates) should raise questions about whether pharmacotherapy is necessary for all individuals with BP-II disorder. Future trials should examine factors that predict differential response to psychotherapy and medication since the most important question, inevitably, will be what works for whom.

Acknowledgments

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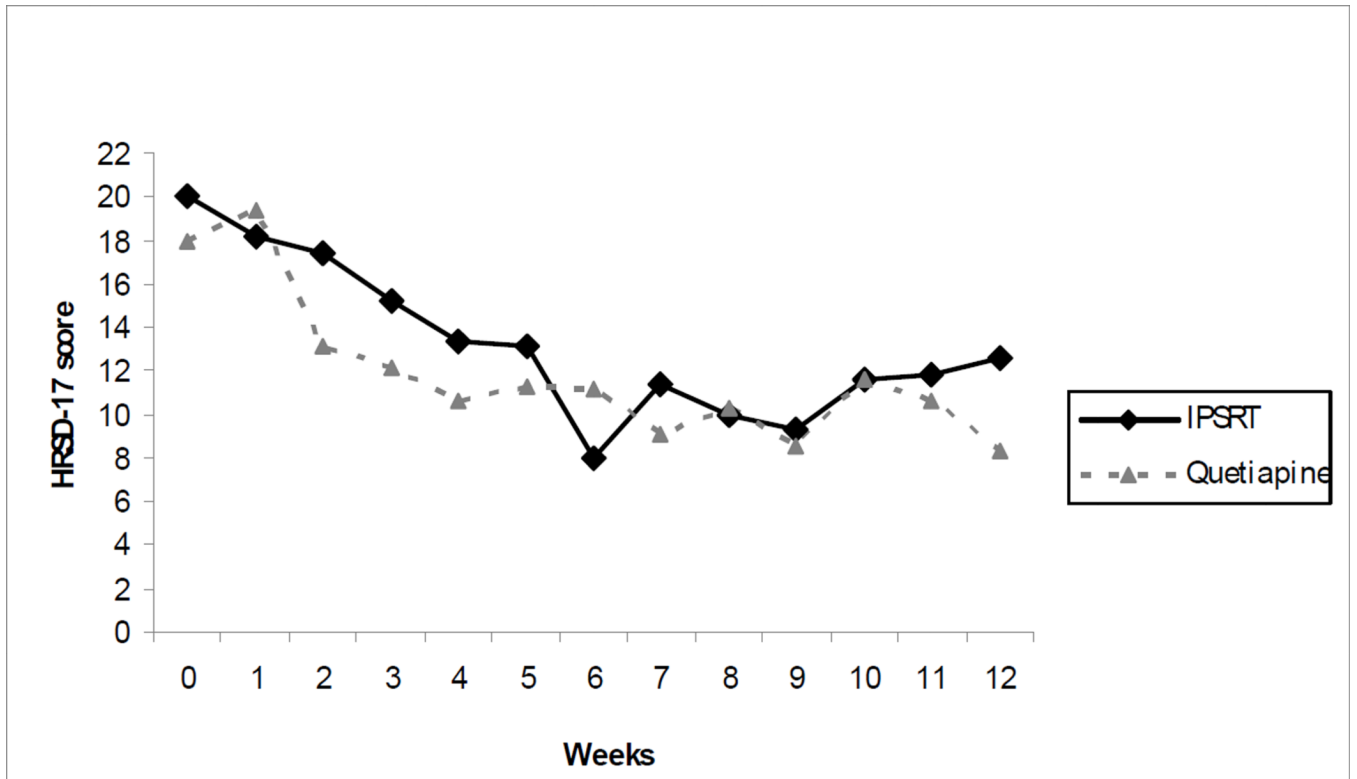
Fig. 1.
Mean 17-item Hamilton Rating Scale for Depression (HRSD-17) scores over 12 weeks.
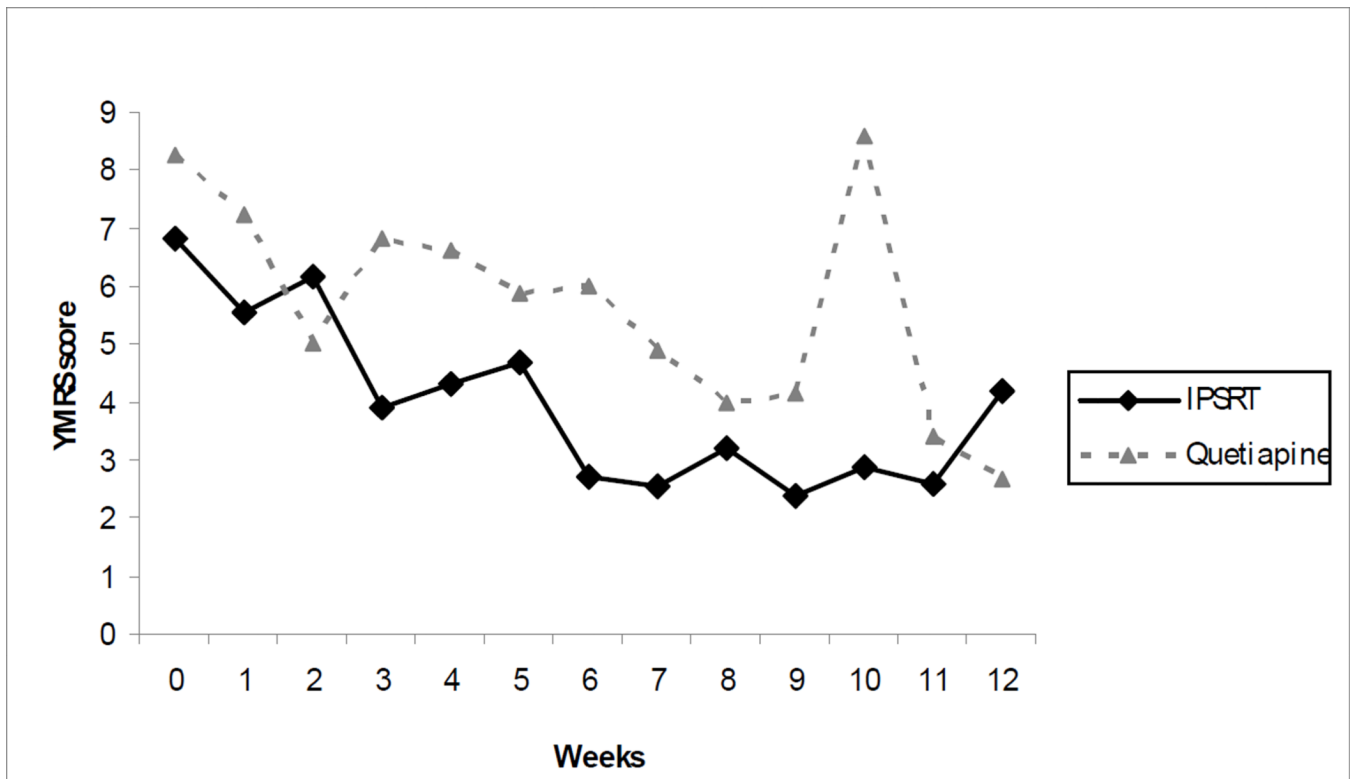IPSRT = Interpersonal and Social Rhythm Therapy.

Fig. 2.
Mean Young Mania Rating Scale (YMRS) scores over 12 weeks. IPSRT = Interpersonal and
Social Rhythm Therapy.

Table 1

Baseline demographic and clinical characteristics of participants assigned to Interpersonal and Social Rhythm Therapy (IPSRT) and quetiapine

Variable	IPSRT (n = 14)		Quetiapine (n = 11)		p-value
	Mean (SD) or n (%)	Median [range]	Mean (SD) or n (%)	Median [range]	
Age, mean (SD)	40.1 (11.7)	36.9 [26.0–63.6]	32.1 (12.8)	25.6 [19.4–59.3]	0.08
Female, n (%)	7 (50)		8 (73)		0.41
White, n (%)	13 (93)		11 (100)		1.00
Education, years, mean (SD)	14.7 (2.1)	14.0 [12–18]	16.1 (2.4)	15.5 [13–21]	0.19
Marital status, n (%)					0.90
Married	5 (36)		3 (27)		
Never married	7 (50)		8 (73)		
Separated or divorced	1 (7)		0 (0)		
Employment, n (%)					
Full time, part time, homemaker	7 (50)		5 (45)		0.83
Student	1 (7)		2 (18)		
Disabled, unemployed	4 (29)		2 (18)		
HRSD-17 score, mean (SD)	20.0 (3.7)	20.0 [15–26]	18.2 (2.1)	18.5 [15–21]	0.27
HRSD-25 score, mean (SD)	25.0 (3.5)	25.0 [20–31]	24.6 (2.7)	25.0 [21–29]	0.44
YMRS score, mean (SD)	6.5 (3.0)	6.5 [2–13]	7.8 (4.2)	6.5 [2–16]	0.58
MADRS score, mean (SD)	25.1 (6.4)	24.5 [14–41]	25.7 (4.8)	25.5 [20–33]	0.75
BAI score, mean (SD)	13.8 (9.1)	15.0 [0–32]	12.2 (7.9)	14.0 [1–25]	0.74
GAF score, mean (SD)	55.1 (2.9)	55.0 [51–60]	58.0 (2.2)	58.0 [55–60]	0.07
Weight (pounds)	187 (56)	177 [106–274]	173 (67)	156 [107–336]	0.35
Duration of index depressive episode (weeks)	53 (100)	23 [2–392]	19 (27)	11 [3–92]	0.11
No. of prior depressive episodes (lifetime)	5.1 (3.7)	4.0 [1–12]	12.3 (17.7)	4.0 [1–50]	0.60
No. of prior hypomanic episodes (lifetime)[a]	3.6 (3.3)	2.0 [1–11]	19.7 (26.3)	6.0 [3–50]	0.15
DSM-IV Axis I comorbidities, n (%)					
Substance use disorder (lifetime)[b]	2 (14)		5 (45)		0.18
Anxiety disorder (current)[c]	8 (57)		5 (45)		0.70

HRSD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; BAI = Beck Anxiety Inventory; GAF = Global Assessment of Functioning.

[a]Excluded individuals reporting *too many episodes to count*, therefore, only eight participants in IPSRT group and three in quetiapine group were included.

[b]Includes alcohol, cannabis, cocaine, hallucinogen/PCP, opioid, and stimulant use disorders.

[c]Includes generalized anxiety disorder, panic disorder, obsessive compulsive disorder, and social phobia.