

Research report

SSRIs as mood stabilizers for Bipolar II Disorder? A proof of concept study

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Abstract

Background: We have previously observed that prescription of some antidepressant class drugs (particularly the SSRIs) is associated with attenuation of the number, duration and severity of both high and low mood states in those with Bipolar II Disorder. We examined whether SSRIs are a mood stabilizer for Bipolar II Disorder.

Method: We report a randomized, double-blind, placebo-controlled cross-over study lasting 9 months in a sample of 10 patients who had not had previous treatment with any antidepressant, antipsychotic or mood stabilizer drug.

Results: Treatment with the SSRI led to a significant reduction in depression severity, percentage of days depressed or high, and percentage of days impaired, when compared with placebo. There was no indication that the SSRI led to a worsening of illness course.

Limitations: Given the small sample size and a weighting to those with a rapid cycling condition, replication with a larger and more heterogeneous sample of those with Bipolar Disorder is required.

Conclusions: This proof of concept study finds preliminary support for the potential utility of SSRIs in managing Bipolar II Disorder, with clear improvements in depression and impairment and some suggested benefit for hypomania.

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1. Introduction

As recently reviewed by [Gijsman et al. \(2004\)](#), the use of antidepressants for those with bipolar depression appears common in clinical practice but is rarely countenanced—at least as monotherapy—in formal treatment guidelines. This view reflects concerns about the possibility of antidepressant drugs inducing switching and rapid cycling in those with Bipolar Disorder. Those

authors noted that all major reviews and guidelines for managing bipolar depression over the past decade have instead recommended the initial prescription of a mood stabilizer as a management strategy alone or before prescribing—after a significant interval—any antidepressant drug, and that no guideline positions antidepressant drugs as first-line treatments. There are some exceptions, however, with the British Association of Psychopharmacology ([Goodwin, 2003](#)) guidelines noting that antidepressants “are effective for treating depression in bipolar disorder” (p. 162). But, as Bipolar Disorder guidelines explicitly or implicitly refer to the management of Bipolar I Disorder, it may be that management

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strategies do not necessarily extrapolate to the management of Bipolar II Disorder (Hadjipavlou et al., 2004).

Over the last few years, we have prescribed SSRIs and the dual action antidepressant venlafaxine as monotherapy in patients with Bipolar II Disorder presenting with an episode of clinical depression, with some intriguing observations. Over extended review periods we have noted a distinct percentage reporting fewer, less severe and less persistent depressive and hypomanic episodes. The latter finding is the more intriguing one and, after reporting a case series (Parker, 2002), we suggested that those medications might have mood stabilizing propensities, in the sense of attenuating or curbing mood swings. This hypothesis prompted this formal proof of concept study of the SSRI antidepressants as having such properties. While there have been several studies examining the efficacy of antidepressant monotherapy (including SSRI medication) for Bipolar II depression (e.g., Amsterdam and Brunswick, 2003), this report is—to our knowledge—the first randomized, double-blind, placebo-controlled study of SSRI medication as a mood stabilizer for Bipolar II Disorder. We specifically assess whether a standard dose of an SSRI antidepressant is more effective than placebo in reducing the frequency, severity and duration of both depressive and hypomanic episodes.

2. Methods

2.1. Subjects

Subjects were recruited from the general community, predominantly through extensive media advertisements. Subjects were eligible if they were aged 18–65 years, had a minimum two-year history of depressive and hypomanic episodes, and had mood episodes (either hypomanic or depressive) occurring at least monthly. The last criterion was to ensure that sample members had mood perturbations at sufficient frequency to expect any true mood stabilizing effect to be identified over the course of a nine-month longitudinal study. Subjects were required to meet DSM-IV criteria for Bipolar II Disorder, with the exception that we did not impose a minimum four-day duration criterion for hypomanic episodes. There is emerging evidence that most hypomanic episodes last 1 to 3 days and that brief hypomania does not differ from longer episodes (Akiskal et al., 2000; Angst et al., 2003; Benazzi, 2001). We further restricted inclusion to subjects who had never previously received any antidepressant, mood stabilising or neuroleptic medication for two principal

reasons. Firstly, we wished to avoid ethical concerns about subjects being required to cease medication. Secondly, we did not wish to risk biases emerging from previous medication exposure—where sample subjects might have either previously benefited from or preferentially ‘failed’ to respond to an SSRI.

Subjects were required to attend multiple assessments, and were unpaid (apart from two subjects who received reimbursement of travel costs). Exclusion criteria included a history of psychotic symptoms during hypomanic or depressive episodes; current suicidal behaviors or ideation; current substantive illicit drug use or alcohol consumption (>30 g/day), and significant personality disorder (as assessed clinically). We further excluded subjects who were breastfeeding or pregnant (or had any intention to become pregnant over the study period), and those who had a history of heart disease, liver disease, epilepsy or seizures. All subjects provided informed written consent prior to study participation. The only external assistance provided for study was the provision (at our request) of identical presentation capsules of escitalopram and placebo by the SSRI manufacturer at no cost to the researchers.

2.2. Design

This study was a randomized, double-blind, placebo-controlled, cross-over trial of escitalopram (10mg) versus placebo (identical presentation) in subjects identified as having Bipolar II Disorder. The nine-month study commenced with a no-treatment baseline period of three months (Baseline Phase) to ensure that subjects met criteria for episode frequency. Subjects compliant with and completing baseline period requirements were then randomized to receive escitalopram or placebo for three months (Phase 2), and then crossed over to receive the alternative compound for the final three-month period (Phase 3). Prior to that cross-over, there was a two-day taper period to avoid potential withdrawal effects, followed by a seven-day wash-out period to avoid carry-over effects from drug to placebo. Subjects were assessed at the start of the study, and every month thereafter for the entire nine-month period. All investigators were blind to drug assignment with randomisation and drug dispensing managed by the hospital pharmacy.

2.3. Measures

Subjects in the study rated their daily mood using a daily rating schedule (Patient Mood Chart or PMC) developed at our Institute for monitoring progress of

patients with Bipolar Disorder. Subjects were instructed to mark the PMC at the end of each day, with recordings representing their mood over the day, and with three categories: ‘OK’ (denoting euthymia), ‘low’ (depression) and ‘high’ (hypomania). If they felt ‘low’ or ‘high’ they charted whether their mood was mild (rated ‘1’), moderate (rated ‘2’) or severe (rated ‘3’, where ‘severe’ was defined as “the worst you have ever been for any episode”). If experiencing a high and a low in one day, they rated the severity of both mood states. Subjects also rated their daily functional impairment, in terms of the impact of their mood on their ability to work, and to interact with colleagues, family and friends. Ratings ranged from ‘0’ for no functional impairment, ‘1’ for slight impairment, ‘2’ for moderate impairment, and ‘3’ for severe impairment. The validity of this measure will be detailed in an independent report.

Subjects also completed the Beck Depression Inventory or BDI (Beck et al., 1961) on a monthly basis to assess depression severity over the previous week, a 46-item Mood Swings Survey (MSS) developed by our Institute to assess features of hypomanic episodes in the previous month, and a 21-item physical symptom checklist assessing the presence and severity (‘mild’, ‘moderate’ or ‘severe’) of drug or placebo side-effects over the previous month. A research psychologist or psychiatrist completed (at monthly intervals) the Hamilton Depression Rating or HAMD (Hamilton, 1960), Young Mania Rating Scale or YMRS (Young et al., 1978) and the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) based on functioning over the previous week.

2.4. Procedures

Volunteers ($n=320$) were initially screened via telephone to determine whether they met inclusion criteria. The majority were excluded on the basis of having previously received psychotropic medication or not being readily able (on geographical grounds) to attend for review over the nine months. In total, 41 (13%) subjects met eligibility criteria and were invited for interview. At this assessment, following screening by a research psychologist who assessed whether individuals had a mood swing pattern meeting DSM-IV criteria for Bipolar II Disorder (assessing all DSM and additional hypomanic symptoms), a psychiatrist undertook a comprehensive clinical psychiatric assessment to determine if the subject was likely to have Bipolar II Disorder (or any alternate condition) and did not meet any study exclusion criteria (with 4 indi-

viduals being excluded on the basis of failure to confirm the diagnosis). Seventeen eligible participants did not attend the initial appointment. For the remaining 20 subjects, study procedures were explained again in full, written informed consent obtained and training in completion of PMC was provided. Of the 20 subjects, 10 withdrew from the study during the baseline 3 months of mood charting and subsequently 10 subjects were randomized to active drug or placebo. Prior to randomisation, a pregnancy test was completed in women to ensure this exclusion criteria was met.

Subjects were required to complete the PMC for the entire nine-month period of the study and to return each chart at their monthly assessment session or by mail. At each monthly session, and following the wash-out period, subjects completed the BDI and MSS, while clinicians rated the HAMD, YMRS and SOFAS. The 21-item checklist of common SSRI side-effects was completed prior to randomization (month 3) to assess baseline symptoms and then at each subsequent review (months 4 to 9). While the majority of monthly assessments were conducted face-to-face, when subjects were not able to attend in person, the assessments were completed over the telephone and questionnaires returned via mail. There was individual variability in the number of days each mood chart was completed for each ‘month’ of the study, depending on the subject’s availability for their assessment interview. The mean number of days the mood chart was completed for all subjects at each assessment point in the study was 31 days.

Each subject was reviewed by a psychiatrist prior to randomization (month 3), and at months 4, 6, 7 and 9 to check on progress and to discuss SSRI side-effects and withdrawal symptoms. At the end of each monthly assessment period, compliance was determined by counting returned tablets.

2.5. Data analysis

To manage the multiple testing occasions, scores on HAMD, YMRS, SOFAS and MSS were averaged across the three time points for each phase of the study. Consequently, there were three mean scores: Baseline mean (months 1, 2 and 3), Phase 2 mean (months 4, 5 and 6) and Phase 3 mean (months 7, 8 and 9). For the PMC, the following variables were calculated for each of the three phases of the study: (i) average severity of PMC highs, lows and impairment, (ii) percentage of days rated high, low and impaired, (iii) percentage of days rated ill (high or low), (iv) average

severity of days rated ill, (v) number of episodes of highs, lows and impairment, (vi) number of episodes rated as ill (high or low), and (vii) longest episode of highs, lows and impairment.

As there was individual variability in the number of days rated, the average and percentage variables (i–iv above) were calculated by dividing the total (either severity or number of days) by the number of days rated for that month. To calculate the number of episodes and longest episodes (v–vii above), the shortest number of days rated for the ten subjects at each time point was assigned. Thus, if three subjects had rated 28, 30 and 32 days for month one, these variables would be calculated based on the first 28 days rated for all subjects.

The SPSS (version 13) statistical software package was used to analyse data using an intention to treat procedure. The principal analyses involved repeated measures Analysis of Covariance (ANCOVA) with group (SSRI first vs placebo first) and phase (means of phase 2 and phase 3) as the independent factors, mean baseline scores on each measure as the covariate, and the patient and clinician-rated measures of mood and impairment as the dependent variables. Treatment effects were indicated by a significant group by phase interaction. To calculate standardised effect size d holding the covariates constant, the difference scores from Phase 2 to Phase 3 were calculated for the two groups and the resulting means and variances, and covariate by outcome correlations, were entered into an equation for computing d for two-group ANCOVA designs (Cortina and Nouri, 2000). Cohen's (1988) quantification of small, medium and large effect sizes (0.2, 0.5, 0.8) were used as a guide to interpreting the results.

Given the sample size, additional tests were run to ensure the reliability of the findings. Thus, the difference between mean scores at Phase 2 and Phase 3 were calculated and compared for the SSRI first and Placebo first groups using non-parametric Mann–Whitney U tests.

Differences in patient reports of side-effects when on SSRI and on placebo were analysed in two ways. Firstly, the number of subjects reporting each of 21 common SSRI side-effects was compared when subjects were on drug and on placebo using McNemar's test. Secondly, the average severity of side-effects was calculated when subjects were on drug and placebo and compared using Wilcoxon's test. These analyses did not take into account the cross-over design of the study.

In light of the limited power, alpha was set at .05 for all analyses.

3. Results

3.1. Patient characteristics and baseline means

Our 10 subjects (5 female) had a mean age of 29.4 years ($SD=3.8$, range 24–35 years), and an average of 13.7 years of education ($SD=2.6$). At study entry, 6 subjects were depressed and 4 were euthymic. Subjects reported having experienced depressive episodes over a mean interval of 12.9 years ($SD=5.2$, range 4 to 20 years) and hypomanic episodes for a mean interval of 12.2 years ($SD=6.5$, range 2 to 19 years). Three subjects reported a family history of depression, two of Bipolar Disorder and one subject reported a family history of both Bipolar Disorder and depression. All 10 patients completed each of the nine monthly assessments.

To determine whether randomization produced statistically equivalent groups, chi-square tests and t -tests were used. The SSRI first group ($n=6$) was equivalent to the placebo first group ($n=4$) on gender (50% females in both groups), mean age (30.2 vs 28.3) and years of education (13.2 vs 14.5). The means of all baseline measures of mood and functional impairment (averaged across months 1, 2 and 3) were compared for SSRI first and placebo first groups. Only one group difference approached significance, with there being a trend for the SSRI first group to have higher scores on the YMRS when compared to the placebo first group (11.25 vs 6.44, $t=1.92$, $p=.09$). No other differences between groups at baseline were suggested.

3.2. Study nuances

Of the ten subjects, seven correctly guessed (all by reference to distinct change in mood states) their assignment at study completion, two were incorrect and one was uncertain. While remaining blind to drug order, nine of the ten subjects reported that their overall mood was best when on the active drug and one reported their mood as being best on placebo. Two of the ten subjects in the study admitted to breaching the protocol. Of those two, one admitted (at review in the final month of Phase 3) to taking high levels of alcohol and marijuana during much of the study, while the second, in response to judging that she was receiving some benefit from the study drug at month 8, had increased the dose to two tablets per day and, in the final month, consulted a psychiatrist and been commenced on sodium valproate. Neither showed any evidence of improvement across the study, but their data are included in all analyses reflecting the intention to treat study design.

Rates of compliance were estimated by counting returned tablets and dividing the number of tablets taken by the number of days on the study drug $\times 100$. In Phase 2 of the study there was a mean compliance rate of 93.5% (SD=7.0, range 77.0–100%) and, in Phase 3, a mean of 83.8% (SD=20.4, range=44.3–100%).

3.3. Treatment effects—qualitative analyses

Fig. 1 graphs PMC severity ratings for highs and lows over the nine months of the study for each of the ten subjects, presented according to the suggested impact of the active drug and the placebo. The scores above the midpoint represent mild, moderate and severe highs, while those below the midpoint represent mild, moderate and severe lows. It should be noted that the lows were recorded as negative values for ease of interpretation of these graphs. There are four suggested patterns of response: those who appeared to show distinctly greater improvement to the SSRI than to the placebo (subjects 1, 2, 4, and 7), those who showed a moderately superior response to the SSRI (subject 5), one who showed a marginally superior response to the SSRI (subject 9), and those who showed no differentiation (subjects 3, 6, 8, and 10) on the SSRI. Subjects 1, 4, and 7 show a clear reduction in the frequency, severity and duration of both hypomanic and depressive episodes while on the SSRI as compared with placebo, while Subject 2 showed a clear reduction in frequency of hypomanic (but not depressive) episodes on the SSRI. The two protocol violators, Subjects 3 and 6, were in the no differential pattern group.

3.4. Treatment effects—quantitative analyses

Table 1 presents the means, standard deviations, treatment effects and effect sizes for each of the variables at each phase of the study for the SSRI first and placebo first groups. For depression, a significant group by phase interaction and a large effect size was found for HAMD with mean severity scores being significantly lower when subjects received SSRI than placebo for both groups. The interaction for the PMC-rated percentage of days low approached significance, with a trend for subjects to show fewer days depressed when receiving the SSRI when compared to placebo, and a medium effect size observed. For the BDI, the interaction was not significant and a small effect size was found, while for the remaining three PMC depression variables, the interactions were not significant, but medium effects were found for two variables. There were no main effects for group or phase for any of

the six depression variables. For measures of hypomania, there was no significant group by phase interaction or main effects for the YMRS or any of the PMC variables. Only one small effect size was observed, for mean longest episode of impairment.

There were three findings that reached or approached significance on the functional impairment measures. The interaction approached significance for the SOFAS, with significantly higher functioning reported when subjects were receiving the SSRI than when receiving placebo, and a medium effect size observed. For the PMC variables, a significant interaction and large effect size emerged for the percentage of days impaired, with significantly fewer days reported as impaired on SSRI when compared with placebo for both groups. The interaction approached significance for PMC-rated number of episodes impaired, with fewer episodes reported when subjects were on SSRI compared with placebo, and a medium effect size. There was a non-significant interaction and small effect size for mean severity of highs and longest episode of highs. No group or phase effects emerged for any measure of functional impairment.

For the additional PMC variables related to illness, the percentage of days ill (either high or low) showed a significant group by phase interaction and moderate effect size. Significantly fewer days were rated as ill when subjects were on SSRI compared to the placebo for both groups. The interactions for mean severity of illness and number of episodes ill did not reach significance but moderate effect sizes were found. Again, no group or phase effects emerged.

Using non-parametric Mann–Whitney *U* tests to compare the groups on differences between Phase 2 and Phase 3 scores, a similar pattern of findings was obtained to those arising from the ANCOVAs. For depression variables, the mean difference scores between SSRI first and placebo first groups approached significance for the HAMD ($z=1.71$, $p=.09$) and PMC-rated percentage of days low ($z=1.71$, $p=.09$) measures. For functional impairment, the group difference approached significance for the SOFAS measure ($z=1.92$, $p=.06$), and reached significance for PMC-rated number of episodes with impairment ($z=1.93$, $p=.05$) and PMC-rated percentage of days impaired ($z=2.13$, $p=.03$). For PMC-rated illness variables, the group differences for percentage of days ill approached significance ($z=1.71$, $p=.09$).

3.5. Side-effects

Using Wilcoxon's Test to analyse subjects' mean severity ratings of 21 SSRI side-effects while on drug

and placebo, one symptom approached significance. There was a trend for subjects to report higher severity of sexual dysfunction on the SSRI when

compared with placebo (0.83 vs 0.33, $z=1.84$, $p=.07$). Using McNemar's Test to compare the frequency of reports of side-effects while on drug

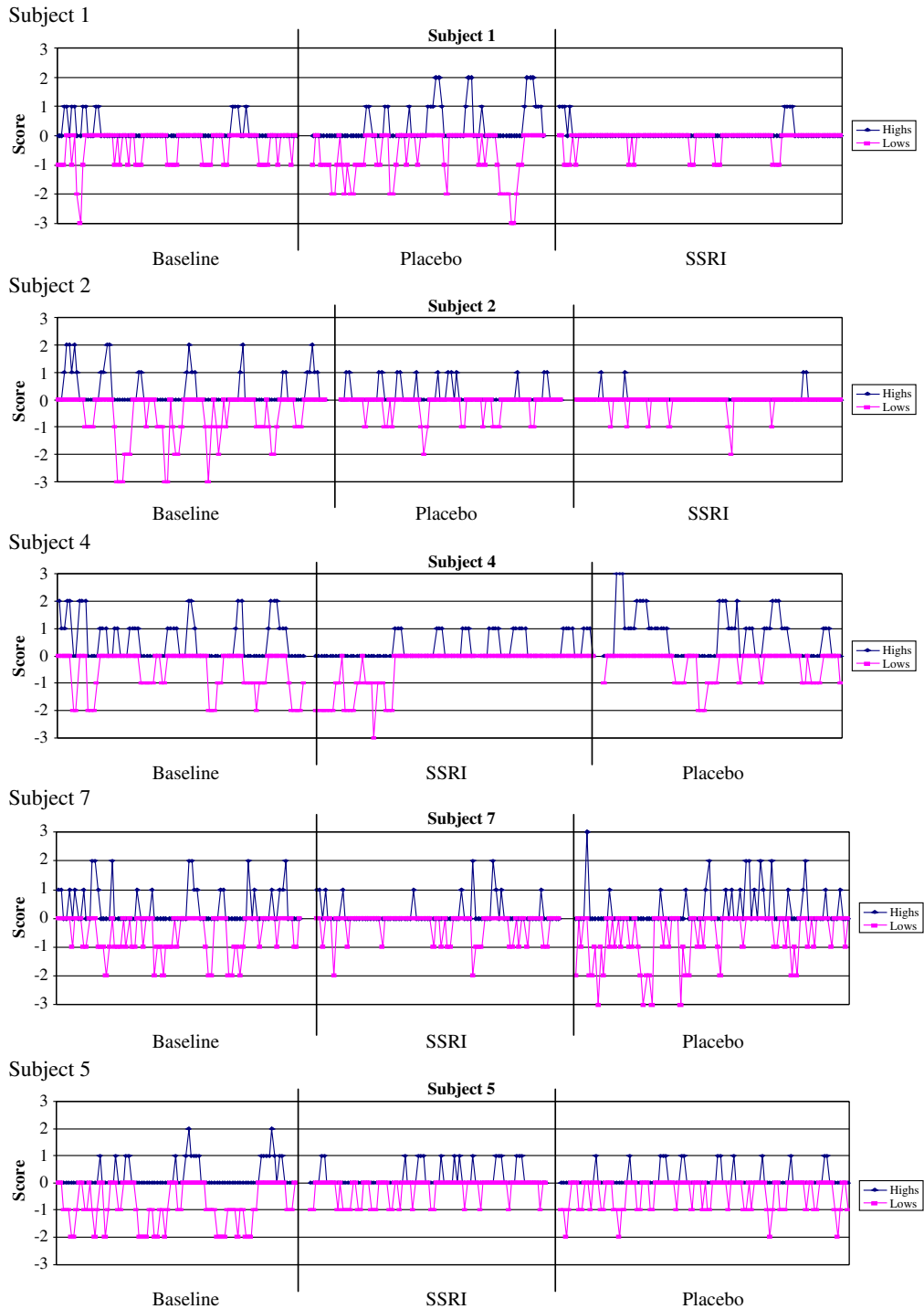


Fig. 1. Graphs of severity of depressive and hypomanic episodes over the three phases of the study for each of the ten subjects, ranked in order from distinct SSRI benefit to no benefit.

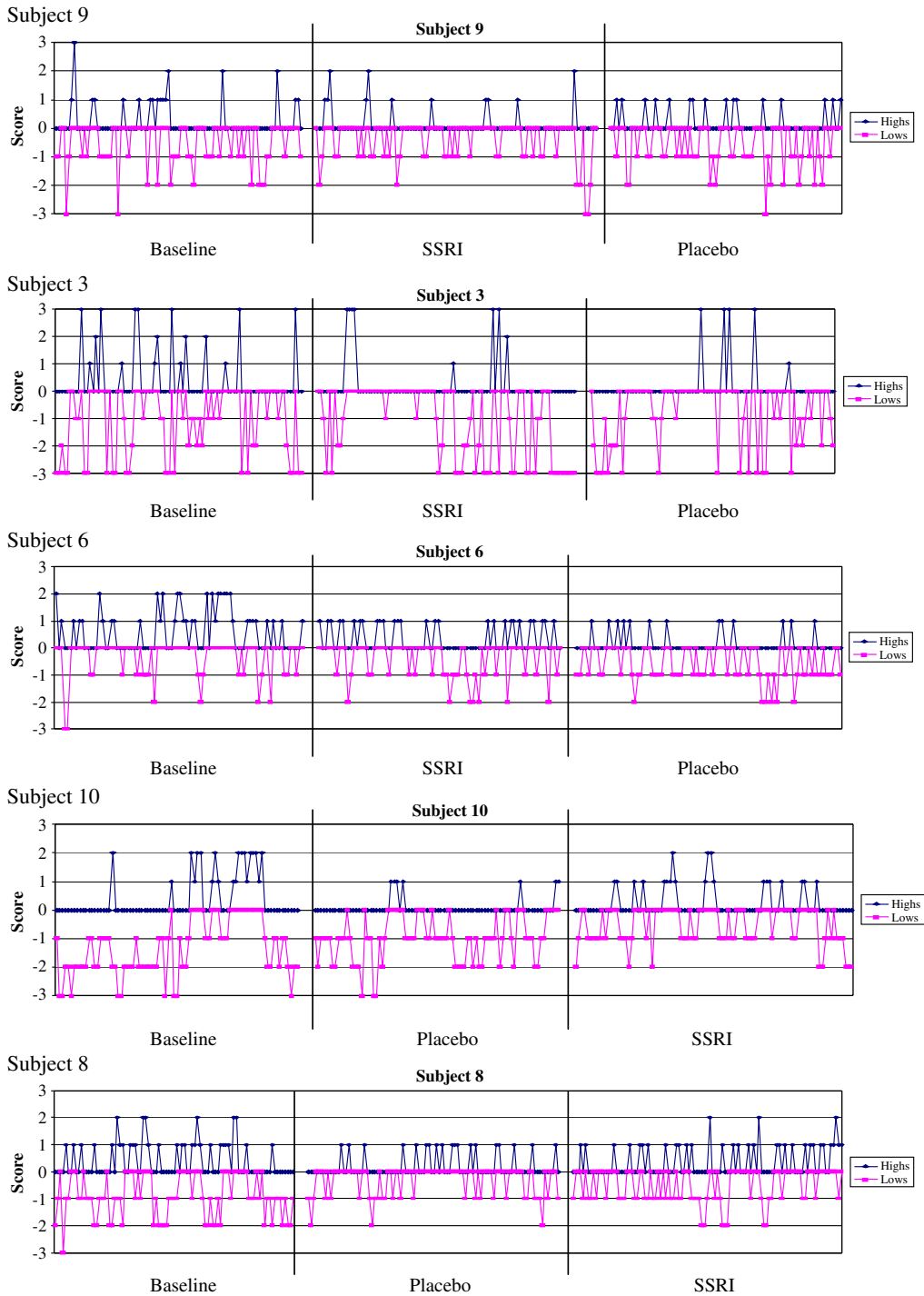


Fig. 1 (continued).

versus placebo, no significant differences were found. It should be noted that small sample sizes make statistical analyses of side-effects problematic and, while

failing to reach statistical significance, six symptoms were reported more commonly by subjects when on SSRI medication than placebo (and baseline): loss of

Table 1

Means, standard deviations, interactions and effect sizes for depression, hypomania and impairment variables at each phase of the study for the SSRI first and placebo first groups

	SSRI first (N=6)			Placebo first (n=4)			Group × phase F	Signif P	Effect size d
	Baseline	Phase 2 (SSRI)	Phase 3 (Placebo)	Baseline	Phase 2 (Placebo)	Phase 3 (SSRI)			
<i>Depression</i>									
HAMD	12.75(4.47)	7.94 (4.90)	12.33 (3.98)	15.06 (8.41)	12.42 (6.85)	8.00 (5.88)	8.64	.02	1.07
BDI	25.72 (5.81)	14.50 (7.73)	18.94 (5.76)	21.50 (11.56)	15.08 (9.05)	13.00 (12.59)	0.96	.36	0.38
PMC—percent days low	41.73 (10.89)	30.94 (8.62)	40.24 (8.17)	52.00 (19.97)	39.46 (20.87)	27.27 (19.51)	4.20	.08	0.71
PMC—mean severity (0–3)	0.62 (0.24)	0.48 (0.34)	0.55 (0.17)	0.78 (0.42)	0.52 (0.35)	0.32 (0.24)	1.22	.31	0.48
PMC—number of episodes	4.39 (1.64)	3.83 (1.44)	5.11 (1.54)	3.25 (1.00)	3.58 (0.63)	3.25 (2.25)	3.04	.13	0.61
PMC—longest episode (days)	5.33 (1.96)	2.89 (1.12)	3.89 (0.72)	7.92 (5.09)	5.33 (3.19)	3.25 (1.60)	3.43	.11	0.76
<i>Hypomania</i>									
YMRS	11.25 (4.03)	5.39 (3.34)	6.67 (8.41)	6.44 (3.64)	8.17 (7.54)	6.75 (7.81)	0.61	.46	0.15
Mood swings survey (MSS)	24.38 (4.38)	14.06 (9.59)	16.31 (10.34)	23.00 (11.19)	12.67 (7.00)	12.42 (14.15)	0.06	.81	0.11
PMC—percent days high	26.16 (10.64)	18.04 (9.56)	19.86 (15.40)	23.43 (7.01)	16.99 (6.39)	15.80 (12.51)	0.04	.84	0.10
PMC—mean severity (0–3)	0.38 (0.15)	0.21 (0.07)	0.27 (0.23)	0.31 (0.11)	0.19 (0.09)	0.17 (0.14)	0.03	.88	0.15
PMC—mean number of episodes	3.50 (1.39)	2.67 (1.43)	2.89 (1.29)	2.75 (1.73)	2.75 (1.26)	2.75 (2.28)	0.02	.90	0.07
PMC—mean longest episode	3.39 (1.42)	2.22 (0.40)	3.11 (4.05)	3.42 (1.85)	2.17 (1.11)	1.92 (0.74)	0.47	.51	0.23
<i>Impairment</i>									
SOFAS	76.25 (4.94)	79.17 (6.72)	68.61 (15.44)	74.69 (17.48)	77.92 (10.22)	85.00 (9.33)	4.87	.06	0.77
PMC—percent days impaired	43.37 (14.51)	27.05 (11.35)	42.79 (17.14)	56.52 (19.78)	41.42 (28.74)	28.45 (22.01)	7.94	.03	0.85
PMC—mean severity (0–3)	0.62 (0.27)	0.47 (0.36)	0.56 (0.25)	0.74 (0.30)	0.51 (0.38)	0.31 (0.24)	1.70	.23	0.47
PMC—number of episodes	4.03 (0.95)	2.86 (1.67)	4.28 (1.32)	4.58 (0.74)	3.67 (2.09)	3.08 (2.18)	4.66	.07	0.79
PMC—longest episode (days)	5.69 (2.66)	3.78 (3.04)	4.83 (2.22)	6.92 (3.73)	5.08 (4.05)	3.33 (2.45)	1.99	.20	0.47
<i>Illness (low or high)</i>									
PMC—percent days ill	68.94 (8.55)	48.45 (12.09)	58.97 (10.60)	71.11 (23.50)	57.02 (19.46)	40.25 (29.90)	5.66	.05	0.70
PMC—mean severity of illness (0–3)	0.99 (0.21)	0.68 (0.35)	0.81 (0.18)	1.04 (0.51)	0.71 (0.33)	0.46 (0.36)	2.30	.17	0.51
PMC—number of episodes ill	7.89 (2.17)	6.50 (2.45)	8.00 (2.59)	6.00 (2.54)	6.33 (1.44)	6.00 (4.41)	0.38	.56	0.56

appetite, somnolence, nausea, sexual dysfunction, decreased libido and headaches. No patients required a dose reduction because of side-effects. No subjects discontinued the study because of side-effects or adverse events.

4. Discussion

This study is the first to examine the possible mood stabilizing properties of SSRIs for Bipolar II Disorder. Overall, the findings indicate that, in this sample of

individuals with Bipolar II Disorder, there was a trend for this specific SSRI medication to reduce the severity of depressive episodes and percentage of days depressed, the frequency and severity of episodes rated as impaired, and the percentage of days with either depressive or hypomanic symptoms, when compared with placebo.

Regrettably, the study was underpowered. Study requirements were onerous, particularly in recruiting those who had never received any antidepressant, antipsychotic or mood stabilizing medication in the past, and in requiring subjects to be compliant with study demands for a nine-month period, making recruitment extremely difficult. Given the small sample size, the results of this study should be interpreted with caution. An additional limitation of the study is that the non-flexible dosing may have reduced the capacity of SSRI benefits to be fully identified. Nevertheless, the study design had a number of strengths and we believe the findings allow a number of preliminary conclusions to be made.

There were several novel and advantageous design elements included in this study. Firstly, we developed a self-report measure for daily completion and suggest that this provided far more detailed information than the cross-sectional measures, with the plot for individual subjects being distinctly informative. Many studies of Bipolar Disorder rely on cross-sectional assessment at regular intervals which can be problematic for individuals with a cycling mood disorder, as chance may well dictate whether (at any one review) the individual is high, low or euthymic. While we did employ a number of relatively standard cross-sectional measures of depressed and hypomanic mood states, the self-report measure enabled frequency, duration, severity and cyclicity of symptoms to be assessed closely. Secondly, the nine-month duration of the study enabled patients' mood fluctuation to be assessed longitudinally. Finally, inclusion of a baseline period for the mood monitoring identified all subjects as experiencing mood swings on a relatively frequent basis, and certainly above the study pre-entry criterion rate of one mood swing episode per month, and indicating that all subjects had a rapid cycling Bipolar II Disorder. Such patterns, which may not be that unusual for many with Bipolar II Disorder, further emphasize the importance of obtaining data on a regular basis (here daily) rather than relying on weekly or monthly measurement.

Formal analyses and inspection of individual trajectories indicate that receipt of SSRI medication was associated with a reduction in depression (severity and percentage of days depressed), improvement in functioning (severity, number and percentage of days impaired) and a weak overall trend—albeit distinct for 4

of the 10 patients—for reduction in hypomania, with there being a significant reduction in the percentage of days ill (whether high or low). Concerns held by some clinicians and which are incorporated in formal guidelines for managing Bipolar Disorder (e.g. that prescription of antidepressants to those with Bipolar Disorder cause switching or rapid cycling) were not supported by any formal analysis in the present study, nor were any such trends evident.

Study nuances contributed to some clouding of the data analyses. Graphed and tabulated data show that there was a general trend for subjects to improve from Baseline to Phase 2—irrespective of whether receiving the SSRI or placebo in Phase 2. Specifically, when we examine percentage improvement in measure scores a clear phenomenon favoring the SSRI is evident. In essence, subjects receiving placebo in Phase 2 and SSRI in Phase 3, would improve in Phase 2 from baseline and improve further in Phase 3, both in regard to their lows and highs (although effects were stronger in relation to depression). By contrast, subjects receiving SSRI in Phase 2 and placebo in Phase 3 would improve in Phase 2 and show a 'drift back' in Phase 3. We illustrate that general phenomenon by quantifying percentages of days high and low (as measured by the daily PMC measure). Thus, those receiving placebo first had a 24% improvement in depression from baseline to Phase 2 placebo (and 27% improvement in highs), but their improvement rates from baseline to Phase 3 SSRI were 48% for depression and 33% for highs. Those receiving SSRI first had a 26% improvement in depression from baseline to Phase 2 SSRI (and 31% in highs), but their improvement rates from baseline to Phase 3 placebo were 3% for depression and 24% for highs. We report effect sizes for all our principal analyses to overcome underpowering in replication studies.

In addition to reporting formal analyses, there are other softer indicators arguing for differential advantages to the SSRI. The graphs (Fig. 1) suggest some benefit from the SSRI in seven of the ten subjects for depression, while four of the ten subjects showed differential benefit to the highs while on the SSRI. Such improvement is not trivial. Further, nine of the 10 subjects judged that their mood was better on active drug when the study was complete, while remaining blind to drug order. Apart from the two study protocol violators who were referred back to a treating clinician, following unblinding, 6 of the 8 other subjects stated that they would wish to have their condition treated in future with an SSRI (five with the study drug and one, who judged it as effective but was troubled by sexual side-effects, chose to trial another SSRI).

We suggest that this proof of concept study finds strong indicative support for the potential utility of SSRI medication in those with Bipolar II Disorder, and no evidence that such drugs worsen the course of the illness. Clearly, adequately powered replication studies are indicated, particularly to clarify whether the SSRIs may operate as formal ‘mood stabilizers’ (in impacting on highs as well as on lows) or merely have antidepressant properties in those with Bipolar II Disorder and then attenuating any ‘rebound’ highs. Further, as the individual SSRIs differ, there is a need to determine whether any mood stabilizing potential is an SSRI class effect specific to those SSRIs that are highly serotonergic. We noted earlier that there is wisdom in recognizing that current mood stabilizing strategies used for managing Bipolar I Disorder may not extrapolate to managing Bipolar II Disorder. If a percentage of patients with Bipolar II Disorder were to benefit from an SSRI rather than require a formal mood stabilizer, this may be of some considerable utility in widening the treatment armamentarium for this increasingly recognized condition.

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References

- Akiskal, H.S., Bourgeois, M.L., Angst, J., Post, R., Moller, H-J., Hirschfeld, R., 2000. Re-evaluating the prevalence and diagnostic composition within the broad clinical spectrum of bipolar disorder. *J. Affect. Disord.* 59 (Suppl. 1), S5–S30.
- Amsterdam, J.D., Brunswick, D.J., 2003. Antidepressant monotherapy for bipolar type II major depression. *Bipolar. Disord.* 5, 388–395.
- Angst, J., Gamma, A., Benazzi, F., Ajdacic, V., Eich, D., Rossler, W., 2003. Towards a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar II, minor bipolar disorders and hypomania. *J. Affect. Disord.* 73, 133–146.
- Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. *Arch. Gen. Psychiatry* 4, 561–571.
- Benazzi, F., 2001. Is 4 days the minimum duration of hypomania in bipolar II disorder? *Eur. Arch. Psychiatry Clin. Neurosci.* 251, 32–34.
- Cohen, J., 1988. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed. Erlbaum, Hillsdale, NJ.
- Cortina, J.M., Nouri, H., 2000. *Effect Size for ANOVA Designs*. Sage, Thousand Oaks, CA.
- Gijmsan, H.J., Geddes, J.R., Rendell, J.M., Nolen, W.A., Goodwin, G.M., 2004. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am. J. Psychiatry* 61, 1537–1547.
- Goodwin, G.M., 2003. Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *J. Psychopharm.* 17, 149–173.
- Hadjipavlou, G., Mok, H., Latham, L.N., 2004. Bipolar II disorder: an overview of recent developments. *Can. J. Psychiatry* 49, 802–812.
- Hamilton, M., 1960. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23, 56–62.
- Parker, G., 2002. Do the newer antidepressants have mood stabilizing properties? [letter]. *Aust. N. Z. J. Psychiatry* 36, 427–428.
- Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. *Br. J. Psychiatry* 133, 429–435.