European Psychiatry 28 (2013) 190–196

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Original article

Characteristics of responders and non-responders to risperidone monotherapy or placebo in co-occurring bipolar disorder and anxiety disorder

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ARTICLE INFO

Article history:
Received 4 April 2011
Received in revised form 12 August 2011
Accepted 13 August 2011
Available online 29 November 2011

Keywords:
Anxiety disorder
Bipolar disorder
Co-occurring
Risperidone
Treatment response

ABSTRACT

Clinical characteristics predicting response and remission to psychopharmacological treatment of bipolar disorder (BD) and co-occurring anxiety disorders have been understudied. We hypothesized that non-response to risperidone or placebo in individuals with co-occurring BD and anxiety symptoms would be associated with a more severe clinical course of BD, and certain demographic variables. This study was a secondary analysis of a randomized, double-blind, parallel, 8-week study comparing risperidone monotherapy and placebo in individuals with BD plus current panic disorder, current generalized anxiety disorder (GAD), or lifetime panic disorder ($n = 111$) [31]. We compared clinical characteristics of responders (50% improvement on the Hamilton Anxiety Scale [HAM-A]) and non-responders as well as remitters (HAM-A < 7) and non-remitters in risperidone treatment ($n = 54$) and placebo ($n = 57$) groups. For non-responders in the risperidone group, co-occurring lifetime panic disorder was significantly more common than for non-responders in the placebo group. Apart from this, no significant differences in course of illness or demographics were found either between or across groups for patients with BD and co-occurring anxiety symptoms receiving risperidone or placebo in this acute phase study.

1. Introduction

A growing number of epidemiological and clinical studies have found that bipolar disorder (BD) co-occurs with anxiety disorders at high rates [6]. Lifetime prevalence of a co-occurring anxiety disorder and BD is estimated between 24–86% [8,10,16,22,24]. Reports have examined clinical characteristics of individuals with BD and a co-occurring anxiety disorder. The presence of a co-occurring anxiety disorder may negatively impact the course and outcome of BD, and has been associated with BD illness variables such as early onset [25], severe depression [3], delay in time to remission [5], and poor response to anticonvulsants [10]. BD that co-occurs with anxiety has also been associated with alcohol use disorders [7,34], suicidal ideation and attempts [35,36], and poor quality of life [34].

Several studies have examined the naturalistic treatment of BD with a co-occurring anxiety disorder. Schaffer et al. [29] found that antidepressant use was higher in BD with a co-occurring anxiety disorder than in major depressive disorder without co-occurring anxiety.

Olanzapine alone or with fluoxetine [42], and quetiapine [11], were better than placebo (PBO) in reducing scores on an anxiety measure in individuals with BD depression. When combined with lithium in a single-blind, open study, adjunctive olanzapine or lamotrigine were effective in reducing anxiety symptoms in individuals with BD and co-occurring anxiety [20].

This study is a secondary analysis of a randomized, PBO-controlled investigation [31] of risperidone (RIS) monotherapy for co-occurring BD and lifetime panic disorder or generalized anxiety disorder (GAD) in patients with current anxiety symptoms.

We investigated a set of illness variables including earlier age of onset, longer duration of illness, suicide attempts, having more severe baseline symptoms; and demographic variables such as lower educational and academic achievements, to see if these predicted resistance to RIS or PBO treatment. We also compared

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doi:10.1016/j.eurpsy.2011.08.001

those patients diagnosed with lifetime GAD versus panic disorder to see if differences emerged.

2. Methods

2.1. Study design

This study is a secondary analysis of a randomized, double-blind, parallel, 8-week study comparing RIS monotherapy with PBO in individuals with BD and lifetime panic or GAD currently experiencing significant anxiety symptoms [31].

All hypotheses and definitions were developed prior to data analysis for this manuscript. Namely, the a priori hypotheses considered were that greater severity of illness at baseline, earlier age of onset, a longer duration of illness, age, gender, a history of suicide attempts, mood episode at study entry, and less education would be predictive of a more treatment resistance (less response) and less likelihood for a remission of symptoms.

2.2. Subjects and measures

Individuals aged 18–65 were recruited from three different university-based hospitals. Informed consent was obtained from all participants. Inclusion criteria included DSM-IV criteria for BD I, II or NOS and a lifetime panic disorder or GAD on the Mini International Neuropsychiatric Interview (MINI) [30]. To compare the illness severity between responders and non-responders, participants were assessed with the Clinician Global Improvement Scale for Anxiety (CGI-21 Anxiety) [32], Hamilton Anxiety Scale (HAM-A) [9], the Young Mania Rating Scale (YMRS) [43] the Inventory of Depressive Symptoms (IDS) [28], the Clinical Global Impression Scale for Bipolar Disorder, overall severity (CGI-BD) [37], and the Sheehan Disability Scale – Family (SDS-F; a rating of the individual's level of functioning in terms of family life and responsibilities) [33].

2.3. Definition of response and remission

Prior to data analysis, we chose to define response and remission using the HAM-A because of its broad use and recognition. Clinical response was defined by at least 50% improvement from baseline on the HAM-A. Clinical remission was defined by the presence of a HAM-A score less than 7 [1].

2.4. Statistics

PASW Statistics v.17 was used for all analyses. Chi-square and *t*-tests were used to examine differences in demographic and clinical variables between responders and non-responders as well as remitters and non-remitters while controlling for effects of treatment group (RIS vs. PBO). Analysis of variance (ANOVA) with last observation carried forward (LOCF) was used to examine relationships between treatment response compared to non-response and outcome measures while controlling for treatment group assignment. ANOVA with LOCF was also used to examine relationships between symptom remission compared to non-remission and outcome measures while controlling for treatment group assignment. Bonferroni correction with $P \leq 0.001$ was used to adjust for multiple testing.

3. Results

In the original study, a total of 111 participants were randomized to receive either monotherapy RIS ($n = 54$) or PBO ($n = 57$). Baseline CGI-BD Severity (CGI-S) scores were 4.5 ± 0.5 in the RIS treatment group and 4.4 ± 0.6 in the PBO group. Baseline HAM-A scores were 24.5 ± 9.5 in RIS and 22.2 ± 9.1 in PBO. Mean RIS dosage at week eight was 2.5 ± 1.1 mg/d. At study termination, 40 patients (82%) were taking less than 3 mg/d of RIS.

3.1. Response

3.1.1. Response versus non-response

A total of 103 participants were included in the responder analysis (eight only had baseline HAM-A ratings); of those 61% ($n = 63$) responded to treatment (RIS + PBO) and 39% ($n = 40$) were non-responsive to treatment (RIS + PBO).

There were no significant differences between all group (RIS + PBO) responders and non-responders for age of onset, duration of illness, history of suicide attempts, mood episode at study entry, age, gender, education, lifetime history of panic disorder vs. GAD and severity of baseline symptoms including CGI-BD, HAM-A, IDS, YMRS, SDS-F (Table 1). Responders had higher anxiety scores on the CGI-21 Anxiety at Week 1 ($F = 14.40$, $df = 1$, $P < 0.001$) than non-responders.

3.1.2. Response by treatment group

Of the 63 participants who responded to treatment, 48% ($n = 30$) were in the RIS group and 52% ($n = 33$) were in the PBO group. Of the 40 participants who did not respond to treatment, exactly 50% ($n = 20$) were in the RIS group and 50% ($n = 20$) were in the PBO group.

Response rates were not significantly different between the RIS and PBO groups. There were no significant differences between responders and non-responders in the two groups regarding age of onset, duration of illness, history of suicide attempts, mood episode at study entry, age, gender, education, lifetime history of panic disorder vs. GAD and severity of baseline symptoms including CGI-BD, HAM-A, IDS, YMRS, SDS-F (Table 2).

Responders and non-responders differed on baseline HAM-A scores in RIS and PBO ($F = 13.69$, $df = 1$, $P < 0.001$); responders in the RIS group had lower baseline HAM-A scores than responders in PBO group. However, non-responders in RIS group had higher baseline HAM-A scores than non-responders in PBO group (Table 2). For non-responders in the RIS group, co-occurring lifetime panic disorder was significantly more common than for non-responders in the PBO group ($\chi^2(1) = 10.16$, $P = 0.001$).

3.2. Remission

3.2.1. Remitters versus non-remitters

A total of 103 participants were included in the remission analysis (eight participants were excluded from the remission analysis because they only had baseline HAM-A ratings); of those 26% ($n = 27$) remitted to treatment (RIS + PBO) and 74% ($n = 76$) did not remit in response to treatment (RIS + PBO).

There were no significant differences between all group (RIS + PBO) remitters and non-remitters on baseline scores of clinical symptom measures including CGI-BD overall, HAM-A, IDS-C, YMRS, and SDS-F.

There were no significant differences between remitters and non-remitters in age ($F = 1.360$, $df = 1$, $P = 0.246$), age of onset ($F = 0.060$, $df = 1$, $P = 0.807$), duration of illness ($F = 1.756$, $df = 1$, $P = 0.188$), suicide attempts ($\chi^2 = 1.844$, $df = 1$, $P = 0.174$), mood episode at study entry ($\chi^2 = 3.711$, $df = 3$, $P = 0.294$), gender ($\chi^2 = 0.233$, $df = 1$, $P = 0.630$), fulltime employment ($\chi^2 = 2.671$, $df = 1$, $P = 0.102$), education ($\chi^2 = 0.099$, $df = 2$, $P = 0.952$), and lifetime history of panic disorder ($\chi^2 = 0.029$, $df = 1$, $P = 0.864$) vs GAD ($\chi^2 = 1.154$, $df = 1$, $P = 0.225$).

3.2.2. Remission by treatment group

Of the 27 participants who experienced remission in response to treatment, 37% ($n = 10$) were in the RIS group and 63% ($n = 17$)

Table 1
Demographic characteristics between non-responders and responders within and between the RIS and PBO treatment groups.

	Responders (63) (RIS + PBO)	Non-responders (40) (RIS + PBO)	Statistics
Mean age	36.2 ± 11.5	36.7 ± 14.8	F = 0.035, df = 1, *P* = 0.852
Mean age of onset	18.8 ± 11.0	16.0 ± 12.0	F = 1.451, df = 1, *P* = 0.231
Duration of illness (years)	17.0 ± 10.4	21.1 ± 15.7	F = 2.421, df = 1, *P* = 0.123
Current mood episodes at study entry			
Euthymia	2	2	χ^2 = 4.027, df = 3, *P* = 0.259
Depressive	21	13	
Hypomania/mania	6	9	
Mixed	34	16	
Suicide Attempt			
No	43	23	χ^2 = 0.727, df = 1, *P* = 0.394
Yes	18	14	
Co-occurring			
Panic disorder (life)	46	29	χ^2 = 0.003, df = 1, *P* = 0.954
Panic disorder (curr)	36	25	χ^2 = 0.291, df = 1, *P* = 0.590
GAD (current)	54	36	χ^2 = 0.407, df = 1, *P* = 0.523
Gender			
Female	41	24	χ^2 = 0.271, df = 1, *P* = 0.603
Male	22	16	
Fulltime employment			
Yes	31	14	χ^2 = 1.56, df = 1, *P* = 0.211
No	30	23	
Education			
High school or less	33	19	χ^2 = 0.081, df = 2, *P* = 0.960
College, AA, Bachelor	23	15	
Graduate or Master degree	5	3	

	Responders (63)		Non-responders (40)		Statistics
Treatment Group	RIS (30)	PBO (33)	RIS (20)	PBO (20)	χ2 = 0.056, df = 1, *P* = 0.814
Mean age	35.5 ± 12.6	36.9 ± 10.6	33.8 ± 12.6	39.7 ± 16.5	F = 0.04, df = 1, *P* = 0.841
Mean age of onset	17.6 ± 11.9	19.8 ± 10.2	14.2 ± 9.0	17.6 ± 14.4	F = 1.39, df = 1, *P* = 0.241
Duration of illness (years)	16.8 ± 11.4	17.1 ± 9.6	19.1 ± 14.7	23.0 ± 16.7	F = 2.34, df = 1, *P* = 0.130
Current mood episodes at study entry					
Euthymia	1	1	1	1	χ^2 = 0.000, df = 1, *P* = 0.833
Depressive	9	12	5	8	χ^2 = 0.064, df = 1, *P* = 0.544
Hypomania/mania	1	5	4	5	χ^2 = 1.250, df = 1, *P* = 0.294
Mixed	19	15	10	6	χ^2 = 0.196, df = 1, *P* = 0.449
Suicide Attempt					
No	20	23	11	12	χ2 = 4.027, df = 3, *P* = 0.259
Yes	8	10	7	7	
Co-occurring					
Panic disorder (life)	23	23	19	10	χ^2 = 1.738, df = 1, *P* = 0.140
Panic disorder (curr)	21	15	16	9	χ^2 = 0.199, df = 1, *P* = 0.430
GAD (current)	24	30	17	19	χ^2 = 0.067, df = 1, *P* = 0.482
Gender					
Female	21	20	12	12	χ^2 = 0.009, df = 1, *P* = 0.924
Male	9	13	8	8	χ^2 = 0.310, df = 1, *P* = 0.578
Fulltime employment					
Yes	15	16	7	7	χ^2 = 0.010, df = 1, *P* = 0.920
No	13	17	11	12	χ^2 = 0.106, df = 1, *P* = 0.745
Education					
High school or less	16	17	9	10	χ^2 = 0.006, df = 1, *P* = 0.584
College, AA, Bachelor	11	12	7	8	χ^2 = 0.005, df = 1, *P* = 0.0604
Graduate or Masters	1	4	2	1	χ^2 = 1.742, df = 1, *P* = 0.286

were in the PBO group. Of the 76 participants who did not remit in response to treatment, 53% (n = 40) were in the RIS group and 47% (n = 36) were in the PBO group (χ^2 = 1.940, df = 1, *P* = 0.164).

There were no significant differences in age (F = 1.360, df = 1, *P* = 0.246), duration of illness (F = 1.756, df = 1, *P* = 0.188), or age of onset (F = 0.060, df = 1, *P* = 0.807); in the RIS group, ages at onset of remitters and non-remitters were 11.3 ± 6.5 and 17.7 ± 11.6 years, respectively. In the PBO group, ages at onset of remitters and non-remitters were 22.2 ± 12.2 and 18.0 ± 11.6 years, respectively.

4. Discussion

This is the first analysis of predictors and characteristics of responders and non-responders meeting criteria for BD and anxiety randomized to RIS monotherapy or PBO. No illness variables were found to be predictive of response to treatment with RIS or PBO including age of onset, duration of illness, history of suicide attempts, severity of baseline symptoms, mood episode at study entry, or type of co-occurring anxiety disorder. Furthermore, no demographic variables were found to be predictive of response to RIS or PBO

Table 2
Comparison of mean scores (SD) of various scales at baseline and end of study between non-responders and responders within and between the risperidone (RIS) and placebo (PBO) treatment groups.

Scales	Responders (63)	Non-Responders (40)
CGI-BD, overall		
Baseline	3.84 (0.45)	3.90 (0.38)
End of study[a]	2.56 (1.22)	3.92 (0.84)
Score change[a]	−1.29 (1.30)	0.03 (0.81)
HAM-A (Response ≥ 50% improvement)		
Baseline[b]	23.81 (8.91)	22.82 (10.22)
End of study[a]	10.16 (7.68)	21.46 (9.35)
Score change[a]	−13.65 (9.78)	−1.44 (7.23)
IDS-C		
Baseline	32.32 (10.98)	31.05 (12.67)
End of study[a]	17.62 (13.34)	32.10 (12.88)
Score change[a]	−14.70 (14.42)	0.59 (11.31)
YMRS		
Baseline	12.00 (6.24)	11.66 (6.69)
End of study	6.33 (6.20)	11.04 (8.35)
Score change	−5.67 (9.17)	−0.73 (7.57)
SDS-FI		
Baseline	125.58 (85.63)	116.38 (96.93)
End of study	61.32 (80.91)	123.31 (97.96)
Score change[a]	−66.75 (98.13)	9.90 (83.30)
CGI-21 Anxiety		
1st week[a,c]	2.08 (2.70)	−0.08 (3.03)
End of study[a]	5.21 (4.65)	−0.31 (4.25)
Score change[a]	3.13 (4.93)	−0.23 (4.38)

Scales	Responders (63)		Non-Responders (40)	
	RIS (30)	PBO (33)	RIS (20)	PBO (20)
CGI-BD, overall				
Baseline	3.80 (0.55)	3.88 (0.33)	3.90 (0.31)	3.90 (0.45)
End of study[a]	2.70 (0.78)	2.42 (1.30)	3.95 (1.19)	3.90 (0.91)
Score change[a]	−1.10 (1.25)	−1.46 (1.28)	0.53 (0.71)	−1.66 (0.92)
HAM-A (Response ≥ 50% improvement)				
Baseline[b]	22.33 (8.15)	25.15 (9.48)	28.05 (10.54)	17.60 (6.77)
End of study[a]	11.40 (8.06)	9.03 (7.26)	26.00 (8.65)	17.15 (7.98)
Score change[a]	−10.93 (7.99)	−16.12 (10.69)	−2.47 (8.95)	−0.45 (5.16)
IDS-C				
Baseline	33.60 (10.44)	32.91 (11.57)	31.67 (13.10)	28.50 (12.01)
End of study[a]	20.37 (14.42)	15.12 (11.95)	37.10 (12.79)	26.84 (10.98)
Score change[a]	−11.30 (12.72)	−17.79 (15.34)	3.50 (10.93)	−2.47 (11.16)
YMRS				
Baseline	12.03 (5.98)	11.97 (6.56)	13.80 (6.28)	9.52 (6.53)
End of study	6.32 (5.32)	6.34 (6.98)	11.40 (8.15)	10.70 (8.72)
Score change	−5.72 (7.95)	−5.62 (10.27)	−2.74 (7.54)	1.18 (7.26)
SDS-FI				
Baseline	119.23 (87.66)	131.53 (84.65)	136.40 (105.45)	95.32 (84.76)
End of study	78.68 (94.94)	49.00 (68.26)	157.13 (101.23)	87.07 (83.05)
Score change[a]	−49.27 (93.46)	−79.57 (101.04)	21.13 (71.89)	−2.14 (95.28)
CGI-21 Anxiety				
1st week[a,c]	2.67 (2.69)	1.55 (2.39)	−0.05 (3.03)	−0.10 (2.94)
End of study[a]	4.97 (4.06)	5.42 (5.18)	−0.79 (4.60)	0.15 (3.95)
Score change[a]	2.31 (4.76)	3.88 (5.06)	−0.74 (4.23)	0.25 (4.58)

CGI-BD: Clinical Global Impression Scale for bipolar disorder; CGI-21 Anxiety: Clinician Global Improvement Scale for Anxiety; HAM-A: Hamilton Anxiety Scale; IDS: Inventory of Depressive Symptoms; PBO: placebo group; RIS: risperdone-treatment group; SDS-FI: Sheehan Disability Scale, family impact; YMRS: Young Mania Rating Scale.
[a] Significant between non-responders and responders in two groups ($P \leq 0.001$).
[b] Significant group by response status interaction that non-responders in RIS had significantly higher baseline HAM-A scores than non-responders in PBO ($F = 13.69$, $P < 0.001$).
[c] Data was not collected at baseline.

treatment including age, employment status, education, marital status, gender, and ethnicity.

4.1. Anxiety and bipolar disorder often co-occur

BD often co-occurs with anxiety disorders or clinically significant anxiety symptoms [6,24]. This co-occurrence has been repeatedly demonstrated in epidemiologic [2,6,24], clinical [5,6,22,34], and family populations [6,18]. The relationship is so prevalent that BD with panic disorder has been proposed to be a genetic subtype of BD [18] that may respond to treatment differently than other forms of BD. Henry et al. [10] found not only that 24% of patients with BD also had at least one co-occurring anxiety disorder, but also that patients with both BD and an

anxiety disorder showed a differential response to treatment with anticonvulsants than patients with BD and no co-occurring anxiety disorder.

Researchers have recently begun to investigate predictors of response to treatment in co-occurring BD and anxiety. In an innovative study of the discrepancy between subjective and objective ratings of depression, Rane et al. [26] found that participants with treatment-resistant major depression and co-occurring anxiety tended to have a greater discrepancy between self and clinician ratings of depression at baseline, and that participants with that discrepancy tended to respond to treatment later (after 16 weeks). This might suggest that with a diagnostically complex population, such as those with both BD and at least one anxiety disorder, a long-term treatment trial may be needed to fully explore predictors of treatment response. However, outside of studies like the above and the current analysis, predictors of treatment response in patients with BD and co-occurring anxiety have yet to be thoroughly studied [12]. In the absence of other data on predictors of response in this co-occurring population, it is difficult to compare the results of this analysis to other findings on response predictors for BD with anxiety. However, many researchers have studied predictors of response and non-response to various types of treatment for patients with BD in a range of mood states, if not specifically with co-occurring anxiety. It is valuable in this case to compare the results of the current study to results of other studies on bipolar populations that looked at predictors of response to treatment.

4.2. Comparison to literature on response predictors studied herein

Some studies found that, under different circumstances, variables that this analysis found to be non-predictive could actually function as reliable predictors of response to treatment. For example, unlike our study, Masi et al. [21] found baseline CGI Severity scores to be predictive of non-response to treatment as usual for children and adolescents with BD. However, it is important to note that the Masi et al. [21] study was conducted with children and adolescents, who are reported by some to be more treatment-resistant than adults with BD [23,38].

In a chart review of a state psychiatric hospital, Keck et al. [13] found that patients' responses to acute RIS treatment for BD were predicted by a number of factors, including a shorter duration of illness. However, the present analysis found that duration of illness was not a predictor of RIS treatment response. There are noteworthy differences between the Keck study and our analysis; in particular, Keck et al. [13] evaluated a long-term state hospital refractory, psychotic population, and thus were studying a different patient population than the outpatient BD group reported on here. Additionally, in the Keck et al. [13] study all of the patients diagnosed with BD were on concomitant mood stabilizers, which could affect their response to treatment. The comparison of this study against our analysis does suggest that future studies examining concurrent use of RIS and mood stabilizers may have different findings when looking for response predictors.

Suppes et al. [39] found that age and severity of baseline mania ratings predicted non-response to aripiprazole or PBO, contrary to the findings in the present analysis; however, the study examined in the present analysis excluded patients with extremely high baseline mania ratings, while the Suppes [39] study did not. This suggests that baseline mania may in fact be a predictor of response to treatment, but only above a certain level, and merits further research. Additionally, Kleindienst and colleagues [15] found that a greater number of prior hospitalizations and later age of onset of BD significantly predicted response to prophylactic lithium treatment. Again, those variables were not found to be reliable predictors in this study; however, in future studies on the treatment of BD with co-occurring anxiety, it could be worthwhile to re-examine those variables as possible predictors, based on Kleindienst and colleagues' findings [15].

4.3. Literature on response predictors not studied herein

Some studies identified reliable predictors of response outside of the variables examined in the present analysis. While there were many differences between the methods of following studies and the study examined in the present analysis, future studies could examine whether those response predictors apply to the specific population of patients with both BD and anxiety.

Lipkovich et al. [17] found that psychotic features, presence or absence of a current mixed episode at baseline, number of manic episodes in the year preceding study entry, presence or absence of disruptive-aggressive behavior, and prominence of depressive features at baseline were predictors of response to olanzapine and divalproex in adults with bipolar I disorder in an acute manic episode, although they were unable to predict between patients who responded slowly (≥ 2 weeks) and patients who did not respond at all. In a landmark study, Swann et al. [41] found that the best predictor of lack of response to lithium was the presence of depressive symptoms during an acute manic episode. It would be worthwhile to examine whether those variables also function as predictors in the distinct subset of bipolar patients that were examined in the present analysis. Additionally, similar studies could investigate other predictors that have been identified, including number of prior episodes, the sequence of mood episodes dominating an individual's episode pattern, continuous cycling, and absence of early partial symptomatic improvement [14,15,40].

4.4. Study limitations

There were a number of limiting factors that could partially explain the lack of differences found between groups in this secondary analysis. One key potential limitation was the distribution of mood episode, type of anxiety disorder, and severity of anxiety symptoms between the RIS and PBO groups. Mood episodes at study entry were not matched across groups; in the riseperidone group, mixed episodes were most frequent, but mixed and depressive episodes were equally frequent in the PBO group. This could have influenced rates of response and remission, particularly since mixed episodes are associated with a poorer prognosis [1].

Similarly, differences in baseline severity of anxiety symptoms between the groups could have contributed to the lack of result. In the PBO group, the baseline HAM-A scores of responders were higher than those of non-responders. Higher baseline HAM-A scores would lead to a higher likelihood of achieving the criteria for response (a 50% reduction in anxiety symptoms).

Finally, initial randomization placed more patients with lifetime panic disorder in the RIS group than in the PBO group. Both the original study and this secondary analysis found that co-occurring lifetime panic disorder was more common in non-responders in the RIS group than non-responders in the PBO group. Lifetime panic and agoraphobic symptoms have been associated with poorer response to acute treatment in patients with BD, and may be associated with a potentially distinct genetic phenotype [5,18,19,27]. Thus, higher rates of co-occurring lifetime panic disorder in the RIS group than in the PBO group could have unevenly affected the results in this study [31].

Additionally, some limitations of the original study could have affected the results of this secondary analysis. In particular, the original study used a distinctly shorter treatment period than was used in the other studies cited in this discussion, particularly compared to those investigating a treatment-resistant population

such as patients with both BD and anxiety. The study also used a double-blind PBO trial design; however, there are a number of potential downsides to using this type of design, including but not limited to some patients not receiving treatment in the study, patients or researchers being able to guess which group the patient has been assigned to, or random chance leading to an uneven distribution of treatment among subjects. Moreover, this study examined a monotherapy treatment versus a PBO, while other studies have suggested that RIS may be particularly effective when combined with at least one other medication [13]. This study could potentially have used a design better able to mask the treatment group, evenly distribute treatments, or best utilize RIS, such as a balanced PBO, balanced cross-over, hidden treatment design [4], or comparative effectiveness trial.

5. Conclusion

There were no differences in the severity of clinical course of BD or demographics that could predict response or remission in this secondary analysis of an eight-week, double-blind, randomized trial comparing RIS monotherapy and PBO for co-occurring BD and anxiety. Our results and further studies with other atypical antipsychotics and mood stabilizers are needed to characterize different patients groups and develop therapeutic strategies for patients with bipolar and co-occurring anxiety disorders.

What variables predict treatment response in adults with BD and co-occurring anxiety has yet to be systematically studied [12] and is a topic with significant consequence for patients and clinicians. Future studies should consider investigating the variables that have been found to predict response in other subgroups of BD that were not investigated in this study. Researchers should also consider adjusting the design of studies investing response predictors, including potentially following patients for a longer duration of time in order to capture those who take longer to respond, capturing information on those who maintain response compared to those who experience a recurrence of symptoms, or using a comparative effectiveness or other balanced study design.

Disclosure of interest

During the time period from January 1, 2003 through August 31, 2010, T.S. has received grant support from the Texas Department of Mental Health and Mental Retardation, Abbott Laboratories, AstraZeneca International, GlaxoSmithKline Pharmaceuticals, Janssen Pharmaceuticals, JDS Pharmaceuticals LLC, National Institute of Mental Health, Novartis Pharmaceuticals, Solvay Pharmaceuticals, Stanley Foundation Bipolar Network, Stanley Medical Research Institute, Pfizer Inc., and Wyeth Pharmaceuticals Inc. She served as a consultant or on the Advisory Boards for Abbott Laboratories, American Psychiatric Association, American Psychiatric Institute for Research & Education, AstraZeneca International, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, GR Med Ed Inc., Janssen Pharmaceuticals, JDS Pharmaceuticals LLC, National Institute of Mental Health, Novartis Pharmaceuticals, Orexigin Therapeutics, Pfizer Inc., Schlesinger Medical, Shire Inc., UCB Pharmaceuticals, CME LLC, Consensus Medical Communications, InforMed Direct, Medscape, Solvay Pharmaceuticals and Wyeth Pharmaceuticals. She has received honoraria from Abbott Laboratories, American Psychiatric Association, AstraZeneca International, Center for Medical Knowledge, CME LLC, GlaxoSmithKline Pharmaceuticals, GR Med Ed, Inc., IntraMed, McLean Hospital, National Association for Continuing Education (NACE), Novartis Pharmaceuticals, Pfizer Inc., University of New Mexico, Consensus Medical Communications, Eli Lilly Research Laboratories, Janssen Pharmaceuticals, Medscape, PSYCH CME, University of Arizona, Medical University of South Carolina, CME Outfitters, University of Michigan, and Wolters Kluwer, Pharma Solutions (CNS Drug Supplement). She has served on speaking bureaus for American Psychiatric Institute for Research & Education, Texas Society of Psychiatric Physicians (TSSP), Depression & Bipolar Support Alliance, AstraZeneca International, GlaxoSmithKline Pharmaceuticals, and National Alliance on Mental Illness (NAMI). She has received royalties from Jones and Bartlett (formerly Compact Clinicals) and MBL Communications Inc. She received travel support from AstraZeneca International.

D.V.S. has received grant/research support from Abbott Laboratories, National Institute of Drug Abuse, American Medical Association, National Institute of Health (NIH), Anclote Foundation, Novartis Pharmaceuticals Corp, AstraZeneca, Parke-Davis, Bristol-Myers Squibb Pharmaceuticals Company, Pfizer Inc., Burroughs-Wellcome Pharmaceutical Company, Quintiles, Cephalon, Sandoz Phamaceuticals Corporation, Eisai America Inc., Sanofi-Aventis, Eli Lilly & Company, Sanofi-Synthelabo Recherche (LERS), Forest Laboratories, Glaxo-Wellcome, SmithKlineBeecham Pharmaceuticals, GlaxoSmithKline, Tampa Gen.Hosp.–University Psychiatry Ctn., International Clinical Research (ICR), TAP Pharmaceuticals, Janssen Pharmaceutica Products LP, The Upjohn Company, Jazz Pharmaceuticals, Warner Chilcott Pharmaceutical Company, Kali-Duphar Laboratories Inc., Worldwide Clinical Trials, Mead Johnson, Wyeth-Ayerst Pharmaceutical Company, Medicinova, Zeneca Pharmaceuticals, and Merck Sharp & Dohme Ltd. He has received honoraria and travel expenses for lectures/presentations at meetings/symposia/education programs sponsored by all the following organizations: Abbott Laboratories, Mead Johnson, AstraZeneca, Merck Sharp & Dohme, Boehringer Ingelheim Pharmaceuticals, Organon, Boots Pharmaceuticals, Novo Nordisk, Bristol-Myers-Squibb, Parke-Davis, Burroughs-Wellcome, Pfizer Inc., Charter Hospitals, Pharmacia & Upjohn, Ciba Geigy, Rhone-Poulenc Rorer Pharmaceuticals, Dista Products Company, Rhone Laboratories, Eli Lilly, Roerig, Excerpta Medica Asia, Sandoz Pharmaceuticals, Glaxo Pharmaceuticals, Schering Corporation, GlaxoSmithKline, SmithKlineBeecham, Hospital Corporation of America, Solvay Pharmaceuticals, Humana, TAP Pharmaceuticals, ICI, TGH-University Psychiatry Center, Janssen Pharmaceutica, The Upjohn Company, Kali-Duphar, Warner Chilcott, Marion Merrill Dow, Wyeth-Ayerst Laboratories, and McNeil Pharmaceuticals. He has served as a consultant for Solvay Pharmaceuticals, Avera Pharmaceuticals, MediciNova, Jazz Pharmaceuticals, Roche, Cephalon, Alexa, Faxmed Inc, Cortex Pharmaceutical, Parexel International Corporation, Pharmacia, GlaxoSmithKline, Sanofi-Synthelabo Research/Sanofi-Aventis, AstraZeneca, Orion Pharma, Shire Laboratories Inc., Janssen Pharmaceutica Products LP, World Health Organization, Forest Laboratories-NJ, Pierre Fabre-France, Lundbeck-Denmark, Alza Pharmaceuticals-Palo Alto-California, Layton Bioscience-California, Wyeth-Ayerst, Organon Inc., Bristol-Myers-Squibb, Pharmacia & Upjohn, Pfizer Inc., National Anxiety Foundation, SmithKlineBeecham Pharmaceuticals, Philadelphia College of Pharmacy & Science, Abbott Laboratories, Lilly Research Laboratories, Connecticut & Ohio Academies of Family Physicians, CPC Coliseum Medical Center, USF Friends of Research in Psychiatry, Board of Trustees, National Anxiety Awareness Program, Anxiety Disorders Resource Center, American Psychiatric Association Task Force on Treatments of Psychiatric Disorders, American Psychiatric Association Task Force on Benzodiazepine Dependency, The Upjohn Company, National Depressive & Manic Depressive Association, Council on Anxiety Disorders, Division of Drugs & Technology, American Medical Association, Anxiety Drug Efficacy Case, US Food & Drug Administration, Ad Hoc Committee: Treatment Drug & Assessment Research Review, Committee (RRC) of NIMH on Anxiety and Phobic Disorder Projects, American Psychiatric Association Working Group to revise DSM III Anxiety

Disorders Section, US Congress-House of Representatives Committee, ZARS, Eisai, Applied Health Outcomes/xCENDA, Targacept, Cypress Bioscience, Tikvah Therapeutics, Titan Pharmaceuticals, Sepracor, United BioScience (UBS), Takeda Pharmaceuticals, International Society for CNS Drug Development (ISCDD), INC Research, Labopharm, Sanofi-Aventis, Neuronetics. He is a share stockholder for Medical Outcome Systems.

S.L.M. is a consultant to, or member of the scientific advisory boards, and/or a principal or co-investigator on research studies sponsored by Abbott Laboratories, Alkermes, AstraZeneca, Bristol-Myers-Squibb, Cephalon, Eli Lilly Inc., Forest Laboratories, GlaxoSmithKline, Jazz Pharmaceuticals, Marriott Foundation, National Institute of Mental Health (NIMH), Orexigen Therapeutics, Schering-Plough, Shire, and Takeda Pharmaceutical Company. She is also inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and, along with the patient's assignee, University of Cincinnati, Cincinnati, Ohio, has received payments from Johnson & Johnson Pharmaceutical Research & Development, L.L.C., which has exclusive rights under the patent.

J.S.S., V.C., I.S.G. and H.Y. have no potential conflicts of interest.

This research was supported in part by a grant from Janssen Pharmaceutica.

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