Influence of sub-syndromal symptoms after remission from manic or mixed episodes

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Background Sub-syndromal symptoms in bipolar disorder impair functioning and diminish quality of life.

Aims To examine factors associated with time spent with sub-syndromal symptoms and to characterise how these symptoms influence outcomes.

Method In a double-blind randomised maintenance trial, patients received either olanzapine or lithium monotherapy for 1 year. Stepwise logistic regression models were used to identify factors that were significant predictors of percentage time spent with sub-syndromal symptoms. The presence of sub-syndromal symptoms during the first 8 weeks was examined as a predictor of subsequent relapse.

Results Presence of sub-syndromal depressive symptoms during the first 8 weeks significantly increased the likelihood of depressive relapse (relative risk 4.67, $P < 0.001$). Patients with psychotic features and those with a greater number of previous depressive episodes were more likely to experience sub-syndromal depressive symptoms ($RR=2.51$, $P < 0.001$ and $RR=2.35$, $P=0.03$ respectively).

Conclusions These findings help to identify patients at increased risk of affective relapse and suggest that appropriate therapeutic interventions should be considered even when syndromal-level symptoms are absent.

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Recent attention has focused on the need to develop therapeutic strategies that allow patients with bipolar affective disorder to return to a premorbid level of function. Effective therapies are currently available for the treatment of acute manic and depressive episodes, and for prolonging time in remission. However, patients considered to have responded to treatment may nevertheless continue to experience sub-syndromal symptoms that impair functioning and diminish quality of life. This disparity between symptom amelioration and functional outcomes among patients with bipolar disorder has been described by Tohen *et al* (1990*a*) and Chengappa *et al* (2005). In a study of first-episode disorder, Tohen *et al* (2000) observed that only 38% of patients achieved functional recovery within 2 years of treatment for an acute manic episode. One factor that may contribute to the difficulty in reaching full functional recovery is the presence of sub-syndromal symptoms that either individually or as an aggregate are not sufficiently severe to constitute a major mood episode, but interfere with functioning.

A recent reassessment of bipolar-spectrum disorders including patients with sub-syndromal symptoms revealed at least a five-fold greater prevalence than found with traditionally defined syndromal diagnoses (Judd & Akiskal, 2003). The persistence of sub-syndromal symptoms in patients with bipolar disorder has been shown to contribute substantially to functional impairment (Gitlin *et al*, 1995; Altshuler *et al*, 2002). Furthermore, sub-syndromal symptoms are associated with an increased risk of relapse (Goodnick *et al*, 1987; Tohen *et al*, 1990a; Keller *et al*, 1992). Keller *et al* (1992) demonstrated that patients prescribed lithium who achieved standard serum levels of the drug were both less likely to develop sub-syndromal symptoms and less likely to experience relapse relative to those who achieved low-range levels, which highlights the role of

adequate therapeutic treatment in the management of these symptoms.

A critical part of developing effective treatment strategies for the management of both sub-syndromal and syndromal symptoms requires a greater understanding of the factors involved in their development. The goal of our *post hoc* analyses was to identify factors that are associated with a greater percentage of time with sub-syndromal symptoms, and to characterise how these symptoms influence outcomes in a randomised double-blind clinical trial of relapse prevention comparing olanzapine and lithium in patients with bipolar I disorder.

METHOD

The details of this randomised double-blind controlled trial have been described previously (Tohen *et al*, 2005) and are summarised briefly here. Participants were at least 18 years old and met DSM–IV (American Psychiatric Association, 1994) criteria for an index manic or mixed bipolar I episode based on the Structured Clinical Interview for DSM–IV (First *et al*, 1995). Prerequisites for study entry were a baseline total score of 20 or more on the Young Mania Rating Scale (YMRS; Young *et al*, 1978) and a history of at least two manic or mixed episodes within the previous 6 years.

The trial consisted of four study periods: screening (2–7 days); open-label co-therapy (6–12 weeks); double-blind taper (4 weeks); and double-blind monotherapy (48 weeks). The starting daily dosages for open-label co-therapy were olanzapine 15 mg and lithium 600 mg. Subsequent dosages of olanzapine could range from 5 mg to 20 mg per day. Investigators were required to optimise lithium dosage and reach a target serum level of 0.6–1.2 mmol/l by week 4 during this period.

Patients who met symptomatic remission criteria for bipolar disorder – a total YMRS score of 12 or below and a total score of 8 or below on the 21-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1959) – during the second study period (co-therapy) were randomly assigned to treatment with either olanzapine or lithium monotherapy. During the third study period, patients remained on their current dosage of randomised treatment and the dosage of the discontinued drug was tapered over

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4 weeks. During the final study period, lithium levels were monitored and the dosage adjusted to maintain serum levels in the therapeutic range 0.6–1.2 mmol/l. All patients randomly assigned to olanzapine also had blood drawn to maintain the study masking. For every outlier report generated for a patient in the lithium group, a sham lithium outlier report was sent to a patient in the olanzapine group. Thus, reports to investigative sites indicating that the lithium dosage should be adjusted did not unmask the randomised assignment.

Illness severity was assessed using the YMRS and HRSD. The categorical definitions of euthymia, sub-syndromal symptoms and relapse (Table 1) are based on previous reports (Yatham *et al*, 2004; Gopal *et al*, 2005; Tohen *et al*, 2005). Relapse and sub-syndromal symptoms were classified globally as bipolar (any mood symptom) and by their respective manic and depressive poles.

Statistical methods

Stepwise logistic regression models were used to identify factors that were significant predictors of the proportion of time spent with sub-syndromal symptoms. The response, percentage time spent with sub-syndromal symptoms, was broken into five categories by quartiles: 0%, 0–<25%, 25%–<50%, 50%–<75% and 75% or more. Linear logistic regression models for these ordinal response data were fitted by the method of maximum likelihood using SAS (version 8.2) PROC LOGISTIC. Categorical explanatory variables included therapy, gender, index episode type (mania or mixed), presence of psychotic features, rapid-cycling status, proneness to depression or mania (defined by the predominant episode type in previous episodes), number of previous bipolar episodes (0–5, 6–9, 10 or more), number of previous manic episodes (0–2, 3–5, 6 or more) and number of previous depressive episodes (0–1, 2–3, 4 or more). Dimensional explanatory variables included age, onset age, duration of illness, baseline YMRS total score, and baseline HRSD total score. The variable therapy was included in all models regardless of statistical significance. The other explanatory variables were entered into the model if they were significant at the $\alpha=0.05$ level and could be removed in a stepwise manner if the least significant effect in the model at a particular step did not meet this level of significance for

staying in the model. Odds ratio estimates and their corresponding 95% confidence intervals were calculated for explanatory variables in the final model.

The presence of sub-syndromal symptoms during the first 8 weeks was examined as a predictor of subsequent relapse. Separate analyses were made for each type of sub-syndromal status (any episode, depressive, manic) and each type of relapse (any episode, depressive, manic). Patients who completed at least 8 weeks of therapy without relapse ($n=340$) were included in the analysis. Additional analyses evaluated the potential impact of the presence of residual symptoms at the outset of the double-blind treatment phase and of the absence of symptoms at the initiation of the double-blind period followed by the emergence of sub-syndromal symptoms during the first 8 weeks on the subsequent risk of relapse: patients were stratified according to the presence (YMRS score 9–14) or absence (YMRS score $\leqslant 8$) of residual symptoms at the outset of the double-blind period. Fisher's exact test was used to test proportions, and relapse incidence rates were characterised by an estimate of the relative risk with 95% confidence limits; estimates were constructed with patients having no time with sub-syndromal symptoms during the first 8 weeks as the referent.

RESULTS

Our analyses included 424 patients with bipolar I disorder. Their baseline demographic and illness characteristics are presented in Table 2. No statistically significant difference was observed between the olanzapine and lithium treatment groups on these baseline measures.

The percentages of patients with sub-syndromal symptoms at any time during the 48-week study are shown in Table 3. Presented in Table 4 are the percentages of time spent with sub-syndromal symptoms categorised by quartiles. There was

no statistically significant difference between therapies with respect to percentage of patients with sub-syndromal symptoms at any time, or the percentage of time with sub-syndromal bipolar symptoms overall or in the individual poles (depression or mania). The mean percentages of time spent with any mood symptom or with manic or depressive sub-syndromal symptoms among patients who experienced them were 27.4% (s.d.=25.7), 26.8% (s.d.=28.7), and 24.4% (s.d.=18.1) respectively (median times 18.4%, 15.4% and 21.5% respectively).

Among patients who completed the first 8 weeks of the relapse prevention phase without a major affective episode ($n=340$), the subsequent rate of relapse for those with bipolar sub-syndromal symptoms was 36.8% (32 of 87) and 29.6% (75 of 253) for those without. Regardless of therapy, the presence of sub-syndromal bipolar symptoms significantly increased the likelihood of relapse into the depressive pole (17 of 87 patients with sub-syndromal bipolar symptoms *v.* 26 of 253 patients without such symptoms; relative risk 1.9, 95% CI 1.09–3.33, $P=0.038$). The presence of sub-syndromal depressive (but not manic) symptoms also increased the likelihood of bipolar relapse (15 of 26 patients with symptoms *v.* 92 of 314 patients without; RR=1.97, 95% CI 1.36–2.85, $P=0.004$) and relapse into the depressive (but not manic) pole (12 of 26 patients with symptoms *v.* 31 of 314 patients without; RR=4.67, 95% CI 2.74–7.97, $P<0.001$). Patients who started the relapse prevention phase without sub-syndromal bipolar symptoms but developed them during the first 8 weeks were significantly more likely to experience bipolar relapse relative to those without sub-syndromal symptoms during the same period (20 of 39 patients *v.* 75 of 253 patients; RR=1.73, 95% CI 1.21–2.48, $P=0.01$). This was especially true of patients with sub-syndromal depressive

Table I Categorical definitions of euthymia, sub-syndromal status and relapse

	Euthymia	Sub-syndromal	Relapse
Mania	YMRS $\leqslant 8$	YMRS 9–14	YMRS $\geqslant 15$
Depression	HRSD $\leqslant 8$	HRSD 9–14	HRSD $\geqslant 15$
Mixed	YMRS $\leqslant 8$ and HRSD $\leqslant 8$	YMRS 9–14 and HRSD 9–14	YMRS $\geqslant 15$ and HRSD $\geqslant 15$
Bipolar disorder	YMRS $\leqslant 8$ and HRSD $\leqslant 8$	YMRS 9–14 or HRSD 9–14	YMRS $\geqslant 15$ or HRSD $\geqslant 15$

HRSD, Hamilton Rating Scale for Depression (21-item); YMRS, Young Mania Rating Scale.

Table 2 Demographic and illness characteristics of the sample

	Lithium group (n=211)	Olanzapine group (n=213)
Gender, n (%)		
Female	114 (54.0)	112 (52.6)
Male	97 (46.0)	101 (47.4)
Mania type, n (%)		
Mixed	12 (5.7)	14 (6.6)
Mania	199 (94.3)	199 (93.4)
Psychotic features present, n (%)	51 (24.2)	58 (27.2)
Rapid-cycling present, n (%)	7 (3.3)	6 (2.8)
Proneness category, n (%)		
Depression	73 (34.6)	72 (33.8)
Mania	138 (65.4)	141 (66.2)
Previous bipolar episodes, n (%)		
1–5	73 (34.6)	83 (39.0)
6–9	71 (33.6)	73 (34.3)
10 or more	67 (31.8)	57 (26.8)
Previous manic episodes, n (%)		
1–2	66 (31.3)	57 (26.8)
3–5	70 (33.2)	92 (43.2)
6 or more	75 (35.5)	64 (30.0)
Previous depressive episodes, n (%)		
0–1	73 (34.6)	89 (41.8)
2-3	73 (34.6)	71 (33.3)
4 or more	65 (30.8)	53 (24.9)
Number of previous bipolar episodes		
Median	7	6
IQR	8	6
Number of previous manic episodes		
Median	4	4
IQR	5	4
Number of previous depressive episodes		
Median	2	2
IQR	3	2
Age, years: mean (s.d.)	42.2 (12.1)	42.6 (13.1)
Age at onset, years: mean (s.d.)	28.2 (10.1)	28.9 (11.5)
Duration of illness, years: mean (s.d.)	13.5 (9.9)	13.3 (10.5)
YMRS total score at visit 1: mean (s.d.)	28.5 (6.1)	27.9 (5.5)
HRSD total score at baseline: mean (s.d.)	5.6 (4.2)	5.4 (4.3)

HRSD, Hamilton Rating Scale for Depression (21-item); IQR, interquartile range; YMRS, Young Mania Rating Scale.

Table 3 Participants with sub-syndromal symptoms at any time during the 48-week study

	Participants, n (%)	
	Lithium group n=211	Olanzapine group n=213
Any mood symptom	83 (39.3)	80 (37.6)
Depression	39 (18.5)	35 (16.4)
Mania	56 (26.5)	48 (22.5)

previous depressive episodes were 1.96 (95% CI 1.04–3.71) times more likely to experience sub-syndromal depressive symptoms relative to those with no or one previous episode, and those with four or more were 2.35 (95% CI 1.21–4.54) times more likely to do so than those with no or one episode ($P=0.03$).

DISCUSSION

Our analyses identified illness characteristics that were associated with a greater amount of time spent experiencing sub-syndromal symptoms in patients with bipolar I disorder, and examined the impact of these symptoms on outcomes. There was no statistically significant difference between the olanzapine and lithium treatment groups with regard to the percentage of patients who experienced sub-syndromal symptoms or in the percentage of time spent with symptoms. Approximately 38% of patients experienced symptoms that fell within the sub-syndromal range of severity, as defined by rating scales, at any time during the maintenance phase of this study. Among these patients, just over a quarter (27%) of the time was spent with sub-syndromal symptoms. These results are consistent with previous reports from non-controlled studies documenting the prevalence of sub-syndromal symptoms in patients with bipolar I disorder (Keitner et al, 1996; Judd et al, 2002; Post et al, 2003). Our findings further extend the view that sub-syndromal symptoms are common and pervasive in bipolar I disorder, even in a population of patients who achieved clinical response from an acute manic or mixed episode and continued to receive treatment for relapse prevention.

Meaningful comparisons between these findings and those of previous reports

symptoms and subsequent relapse into the depressive pole (12 of 25 patients v. 31 of 314 patients; RR=4.86, 95% CI 2.87–8.24, $P<0.0001$). In contrast, patients who had residual sub-syndromal symptoms (any mood) at the outset of the double-blind phase and continued to experience symptoms during the first 8 weeks were not more likely to relapse than those without sub-syndromal symptoms during this period (12 of 48 patients v. 75 of 253 patients; RR=0.84, 95% CI 0.50–1.43, $P=0.60$).

Of the individual factors assessed, presence of psychotic features and a greater number of previous depressive episodes were associated with increased time with depressive sub-syndromal symptoms. Patients with psychotic features were 2.51 (95% CI 1.47–4.30; $P<0.001$) times more likely to experience sub-syndromal depressive symptoms. Patients with two or three

Table 4 Percentage of time spent with sub-syndromal symptoms

	n	Time with symptoms, %				
		0%	0–25%	25–50%	50–75%	>75%
Bipolar						
Lithium	211	60.7	22.3	10.0	5.7	1.4
Olanzapine	213	62.4	22.1	7.0	3.8	4.7
Depression						
Lithium	211	81.5	12.3	4.3	1.9	0.0
Olanzapine	213	83.6	8.5	5.6	1.4	0.9
Mania						
Lithium	211	73.5	16.1	4.7	4.7	0.9
Olanzapine	213	77.5	14.6	2.3	2.3	3.3

with respect to time with sub-syndromal symptoms are difficult to make because of differences in defining criteria, methods of assessment and study design. Notably, for participants in our study who experienced relapse into an affective episode during the study period, only data prior to the event were included in the analyses. It should also be noted that all patients entered this study with an index manic or mixed episode, which may account in part for differences in the distribution of time with symptoms in the two poles relative to studies that involved patients with either manic/mixed or depressive episodes. Indeed, previous studies have reported that patients spend substantially more time with depressive symptoms than with manic symptoms (Judd *et al*, 2002; Post *et al*, 2003; Joffe *et al*, 2004), whereas the distribution of time with symptoms in our study was roughly equal for the manic (26.8%) and depressive (24.4%) poles. Since the polarity of index mood episode is a predictor of the polarity of subsequent relapse (Tohen *et al*, 2003), it is possible that the distribution of sub-syndromal symptoms is similarly dependent on the polarity of the index episode.

Predictors of sub-syndromal symptoms

Of the clinical variables analysed, the presence of psychotic features and the number of previous depressive episodes were associated with increased time spent with sub-syndromal symptoms. Patients who entered the study with psychotic features were more likely to experience a greater percentage of time with sub-syndromal depressive symptoms than those

without such features. This finding is interesting in light of recent reports questioning the prognostic value of psychotic features in bipolar disorder with respect to illness severity and treatment response (Keck *et al*, 2003). In a study by Swann *et al* (2004) the presence of psychotic features was associated with greater overall functional impairment, but was not correlated with higher baseline mania scores or altered treatment response. On the other hand, a study by Tohen *et al* (1990*b*) identified the presence of psychotic features during the index episode as a predictor of shorter time in remission.

A greater number of previous depressive episodes was also associated with a greater percentage of time spent with sub-syndromal depressive symptoms, which is in accordance with a previous report by Post *et al* (2003). These findings also extend previous reports that a greater number of previous affective episodes increases the risk of subsequent relapse (Kessing *et al*, 2004).

Predictors of relapse

In our study the presence of sub-syndromal symptoms during the first 8 weeks of the relapse prevention phase was associated with a significantly greater likelihood of subsequent relapse, particularly into the depressive pole. This finding agrees, in part, with previous studies that have reported an increased risk of relapse associated with sub-syndromal symptoms (Goodnick *et al*, 1987; Tohen *et al*, 1990*a*; Keller *et al*, 1992). However, the presence of depressive sub-syndromal symptoms was predictive of depressive relapse, whereas there was no corresponding relationship between

sub-syndromal manic symptoms and manic relapse. In contrast, in a study of relapse prevention with lithium, Keller *et al* (1992) reported in a non-controlled study a stronger association between manic sub-syndromal symptoms and manic relapse relative to the depressive polarity. It is not clear what factors account for these discrepant results; however, it is possible that the use of olanzapine and lithium in combination to treat the acute episode, and monotherapy during relapse prevention, might have contributed to our results. Further analyses of sub-syndromal symptoms during the first 8 weeks of the monotherapy phase that differentiated residual sub-syndromal symptoms (i.e. symptoms from the index episode that had not resolved completely) from newly emerged sub-syndromal symptoms yielded intriguing results: the emergence of sub-syndromal symptoms (in particular sub-syndromal depressive symptoms) was associated with significantly greater risk of subsequent relapse into the depressive pole, whereas the presence of residual symptoms was not. This finding suggests that the longitudinal assessment of symptom severity, as opposed to just cross-sectional assessment, might better determine the risk of subsequent relapse.

Limitations

There are several limitations to these analyses that warrant discussion. Patients in this study were required to achieve remission from an acute manic or mixed episode to be included in the relapse prevention phase of the trial; thus, this population consisted of patients who responded to combined olanzapine and lithium treatment and who might not be representative of the general population of people with bipolar I disorder. A related limitation is that our results may not be generalised to patients who are unable or refuse to participate in clinical trials. It should be noted, however, that in contrast to naturalistic studies, the analyses of data from our randomised clinical trial were adjusted for pharmacological treatment. Another limitation is the relatively short follow-up period of only 1 year, which may not characterise the full longitudinal course of bipolar disorder.

Our findings provide prognostic value in terms of identifying patients at increased risk of affective relapse. Given that the presence of sub-syndromal symptoms is

associated with significant functional impairment (Tohen *et al*, 1990*a*; Altshuler *et al*, 2002) and incurs large social and economic health costs (Bauer *et al*, 2001; MacQueen *et al*, 2003), appropriate pharmacological and non-pharmacological therapeutic interventions should be considered even in the absence of symptoms at the syndromal level.

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