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THESIS:

Predictive value of bipolar-spectrum clinical features in a large cohort of fluoxetine treated patients with major depressive disorder

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Predictive value of bipolar-spectrum clinical features in a large cohort of fluoxetine treated patients with major depressive disorder

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Abstract

Objective: The presence of unrecognized bipolar disorder or "bipolar spectrum" features has been suggested to contribute to poor treatment response in major depressive disorder. We aimed to investigate the association between putative bipolar

spectrum features and clinical outcomes in a cohort of fluoxetine-treated patients with MDD.

Method: N= 602 outpatients aged 18-65 years with major depressive disorder recruited at 2 academic medical centers first entered a 12-week phase of open-label treatment with fluoxetine titrated up to 60mg/day. Patients who met the response criteria by week 12 entered the second phase of the study during which they were double-blindly randomized either to continue the same fluoxetine doses to which they had responded or to take placebo, for 52 weeks or until the occurrence of a relapse. The following clinical features suggestive of bipolar illness were selected for analysis: a history of early onset and recurrent depression, baseline atypical depressive features, irritability, psychoticism, suicidality, interpersonal sensitivity, comorbid anxiety disorders, and substance abuse/dependence. These measures were condensed into a summary score of bipolarity ranging from 0 to 10 points. We considered as primary outcomes time to response, remission, and discontinuation during acute treatment and time to relapse in the second phase of the study, utilizing survival analyses.

Results: Higher scores on the summary measure of bipolarity were not associated with differential acute treatment outcomes. They were significantly associated with a shorter time to relapse ($p = 0.016$). The median time until first recurrence was 52.0 weeks in the group with lower scores vs. 12.0 wk in the group with higher scores.

Conclusion: Bipolar spectrum features may be associated with shorter time to recurrence in MDD patients after recovery, suggesting some predictive validity for this measure.

Keywords: bipolar spectrum, major depressive disorder, treatment response, recurrence

INTRODUCTION

The bipolar spectrum concept, which posits a symptomatologic continuum between major depression and bipolar disorder[1-7], aims to recognize a hidden bipolar diathesis in depressed patients. In clinical research, a long list of symptoms and/or psychopathological dimensions has been targeted as factors suited to distinguish individuals with unipolar depression from those at risk of developing a hypo-/manic episode. Among the features of disease course and characteristics, an early age of onset[8-11], a recurrent course of depression[9-12] and a family history of bipolar disorder[11,13] are consistently cited as indicators of ”bipolarity” in depressed subjects. Among individual symptoms, reported differences in the clinical presentation of unipolar depression versus bipolar depression are less reliable and less consistent. However, compared to unipolar depression, subjects with bipolar disorder have a higher prevalence in psychotic symptoms[13-20], psychomotor disturbance/retardation[13, 21, 22], intraepisode irritability, anger, agitation and restlessness[23-27], mood lability[28, 29], suicidality[11, 30] and atypical features[18, 24, 31-34] . Moreover, anxiety disorders and substance abuse/dependence

comorbidity have been more closely associated to bipolarity compared to unipolar depression[35-42].

As antidepressants may be less effective in treating individuals with bipolar depression compared to those with major depressive disorder[43-46], some authors suggest that unrecognized bipolar disorder contributes to apparent treatment resistance in individuals diagnosed with major depression[47-49]. To our knowledge, this has not yet been tested in large cohorts. Therefore, we constructed a summary measure of ten putative bipolar markers and hypothesized that higher scores on this measure would be associated with poorer treatment outcomes in depressed subjects. We examined a large cohort of fluoxetine-treated patients in which fluoxetine responders were randomized to continue fluoxetine or cross over to placebo.

Method

The present study was conducted at the New York State Psychiatric Institute and the Depression Clinical and Research Program at Massachusetts General Hospital. The protocol was approved by the ethics committee at both sites, and all participants provided written informed consent. Patients eligible for inclusion were outpatients aged 18-65 years who met the Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Text Revision (DSM-III-R) criteria for a current major depressive episode. Diagnoses were confirmed by the Structured Clinical Interview for DSM-III-R Axis I Disorders—Patient Edition[50]. It was not necessary that patients met any minimum score for severity of depressive symptoms in order to be included in the study. Exclusion criteria included pregnancy or breast-feeding; a significant risk of suicide; a lifetime history of any organic mental disorder, psychotic disorder, or mania; an unstable general medical condition, a history of seizures or of a neurological disorder that significantly affects central nervous system functioning; a history of substance abuse/dependence other than nicotine dependence in 6 months prior to enrollment; current consumption of medications that may induce or worsen

depression; clinical or laboratory evidence of hypothyroidism without adequate and stable replacement therapy; or a history of nonresponse to an adequate trial of a selective serotonin reuptake inhibitor (as defined by a 4-week trial of ≥40 mg of fluoxetine or the equivalent per day).

The study consisted of two phases. After a 1-week medication-free washout period, patients who still met inclusion criteria and had not significantly improved entered a 12-week phase of open-label treatment with fluoxetine. This phase included weekly treatment visits with a research psychiatrist for the first 6 weeks, biweekly for the next 4 weeks, and two last visits for the remaining two weeks. Target fluoxetine doses were as follows: 10 mg/day for the first week, 20 mg/day for weeks 2–4, 40 mg/day for weeks 4–8, and 60 mg/day for weeks 5–12. However, further dose adjustments were allowed based on tolerability. The primary research outcome was change in 17-item Hamilton Depression Rating Scale (HAM-D) [51].

Patients whose HAM-D decreased by at least 50% by week 12 were eligible to enter the second phase of the study, during which they were randomized either to continue the same fluoxetine treatment or start a similar dosing schedule of placebo. Fluoxetine and placebo capsules were matched in

size, shape, color, sheen, and texture to ensure blinding. Phase two continued for 52 weeks, or until the occurrence of a relapse. This second study period was divided according to convention, between a 6 month continuation phase and a 6 month maintenance phase. Treatment compliance was monitored by counting returned capsules at subsequent study visits; subjects who were deemed poor adherers by the treating study physician were dropped from the study.

Summary Score Definition and Outcome Measures

After reviewing the literature on indicators of "bipolarity" in depressed patients, three experienced clinicians (MF, RP, FC) selected clinical characteristics suggestive of a bipolar spectrum illness that could be assessed in this sample. Specifically, these characteristics included a history of early onset ($\leq$ 21 years old), recurrent depression, baseline atypical depressive features, psychomotor retardation, irritability, psychoticism, suicidality, interpersonal sensitivity, current or past comorbid anxiety disorders, and past substance abuse/dependence (family history of bipolar disorder was not collected and so could not be included). These measures were condensed into a summary score ranging from 0 to 10 points.

Higher scores on the summary measure would indicate higher suspicion of bipolarity.

Assessment procedures

Diagnoses of major depression, current or lifetime anxiety or eating disorders and past substance use (current substance use was ruled out before enrollment) were established using the Structured Clinical Interview for DSM-III-R, clinician version (SCID-CV) [52]. Subjects score one point on the summary measure if they present 2 or more anxiety or eating disorders from among Panic Disorder, Social Phobia, Obsessive-Compulsive Disorder, Post-Traumatic Stress Disorder and Bulimia Nervosa. Subjects scored another point if they endorsed a history of at least 1 past substance abuse/dependence disorders among alcohol, cannabis, opioids, stimulants, cocaine and hallucinogens. Information about early onset of major depressive disorder ($\leq$ 21), recurrent course, baseline atypical features and psychomotor retardation was also obtained from SCID. All available data from SCID and Beck Depression Inventory[53], administered at baseline, were used to assign another point for history of suicide attempts and/or current ascertained suicidal ideation, plans or attempts. The Anger-Hostility section of the Symptom Questionnaire[54],

the Massachusetts General Hospital Anger Attack Questionnaire[55], and the Hostility Dimension of Symptom Check List-90 – SCL-90[56] were used to determine the irritability component of the summary measure, with at least 50% of items in one or more of these scales being necessary to warrant a point.

We used the SCL-90 paranoid ideation and psychoticism subscales (at least 50% of items) and item 20 of the Hamilton Scale (≥ 2) to obtain a measure of psychoticism: while current overt psychosis (by SCID) was exclusionary per study protocol, presence of symptoms on SCL-90 or HAM-D was not. Finally, rating from the Interpersonal sensitivity Dimension of SCL-90, interpersonal sensitivity and rejection avoidance items from Columbia Atypical Depression Diagnostic Scale[57] were adopted to evaluate the interpersonal sensitivity point in the summary score.

Primary outcome measures included the time to response, remission, and discontinuation during acute treatment, as well as the time to relapse in the second phase of the study, utilizing survival analyses. Remission and response were defined respectively as a HAM-D-17 rating score ≤ 7 for at least 2 consecutive weeks and as a reduction in baseline HAM-D-17

score by ≥ 50%. Relapse was defined as either having a HAM-D-17 score of ≥ 14 or having met DSM-III-R criteria for major depression for at least 2 consecutive weeks.

Statistical Methods

Primary analysis excluded the subset of patients (N = 26) endorsing a lifetime diagnosis of bipolar II disorder, cyclothymia, or bipolar disorder NOS by the SCID criteria. However, scores in this subset were compared to the remainder of the sample in order to internally validate the summary measure of bipolarity.

Based on sample mean and after visual inspection of distributions, for descriptive purposes we divided the summary measure in two levels, High and Low, depending on a score of ≤ or > 4, respectively. Missing observations of the HAM-D scale were addressed using the Last Observation Carried Forward (LOCF) approach. We used Kaplan-Meier survival analyses to generate survival plots and estimate median time to response, remission, discontinuation and recurrence, with interquartile ranges (IQR). Cox regression model with Wald statistics was adopted to test the effect of the summary score on time to response, remission, discontinuation and relapse as dependent variables, adjusting for baseline depression severity

and for depression severity at time of randomization (e.g. entering phase II) for relapse. Where a main effect of the bipolarity score was identified we looked at treatment (fluoxetine vs placebo) for summary score (Low vs High) interaction.

Summary data are reported using chi-square tests for categorical items and t-test for continuous variables, and displayed as proportions (percentages) and means with standard deviations respectively. Statistical tests of hypotheses were two-sided, with an alpha level of $p \leq 0.05$ and were performed with SPSS (Rel. 11.0.1. 2001. Chicago: SPSS Inc.) and STATA (Rel. 10. 2007. College Station, TX: StataCorp LP) for Windows.

Results

Table 1 shows proportions of patients meeting criteria for each feature included in the summary measure; the most common was thoughts of suicide observed in 351 (55.7%) subjects at study entry. Overall, the mean score on this measure was 3.36 (SD = 1.93); 180 subjects fell into the “High” category and 448 into the “Low” category. As summarized in Table 2, the high group was more likely to be female, single and younger and to have a greater severity of depression at baseline. Notably, the mean score on the summary measure was significantly greater for the cohort (N = 26) with ascertained bipolarity excluded from following analyses in comparison with unipolar patients (N = 602) (Mean = 4.69; SD = 1.93 vs Mean = 3.30; SD = 1.57; t = 3.631 p = < 0.001). Survival analyses showed that a high score on the summary measure was not significantly associated with differential acute treatment outcomes, both in terms of time to response (HR = 1.17, 95% CI = 0.92-1.48; p = 0.20) and remission (HR = 1.12, 95% CI = 0.86-1.46; p = 0.39) (Fig.1), nor was it associated with time to treatment discontinuation for any reason (HR = 0.94, 95% CI = 0.68-1.30; p = 0.71). However, High summary measure scores were significantly associated with a shorter

time to relapse (HR = 1.58, 95% CI = 1.09-2.28; p = 0.016) (Fig. 2). The median time until first recurrence was 52.0 weeks (IQR = 6- NC) in the group with lower scores compared to 12.0 weeks (IQR = 4-NC) in the group with higher scores. Incorporating individual terms for age, sex, marital status, severity of depression at baseline and history of recurrences did not change the hazard ratio by more than 10%. Moreover, history of recurrence was a component of the measure, but was not itself significantly associated with hazard of relapse.

Notably, there was no significant treatment-by-group interaction (HR = 0.96, 95% CI = 0.58-1.61; p = 0.89), suggesting similar results in subjects on fluoxetine or placebo**.**

Discussion

The primary finding of our analysis is the association of high scores on a summary measure of bipolarity with a shorter time to recurrence, but no difference in acute response. A high degree of recurrences was targeted as the core feature of bipolar illness by Kraepelin[58]. Consistent with our results, prior studies suggested that a higher susceptibility to recurrence is both a marker of bipolarity and an adverse outcome linked to soft bipolarity[59-62].

Since antidepressants don't work as well for bipolar depression as for unipolar depression[44, 47-49], some authors argue that an underlying bipolar diathesis or a soft bipolar spectrum could explain treatment resistance in a large proportion of unipolar depressed subjects[47, 49]. Also, many concerns have been raised on the prescription of antidepressants for bipolar depression with many studies reporting an increased risk of hypo-/manic switches, mixed features and suicidality[47, 63-67].

Furthermore, antidepressant use in bipolar disorder has been associated with increased risk of relapses and cycle acceleration in the long term[68-70] and the loss of an initial antidepressant response (i.e. "wear-off" effect) has been

demonstrated to be more common in bipolar than in unipolar depression[71].

Our results are partially consistent with these arguments. They suggest that the effect of greater bipolar loading is not on the acute antidepressant response, but rather on recurrence risk. Importantly, this effect is not due to a recurrent course, per se, because neither a history of recurrence nor other demographic and clinical variables seem to confound the hazard of relapse. Moreover, continuation of antidepressant treatment did not seem to mediate the association between summary measure of bipolarity and risk of relapses. However, a longer follow-up may be more appropriate to ascertain the impact of antidepressant on cycling.

Of note, this analysis is not intended to address the important related issue of depressive mixed states and was not designed to measure intra-depressive hypo-/manic symptoms or mixed features such as agitation, crowded thoughts, or other intraepisode hypomanic symptoms. In this regard, intradepressive mixed features have been reported to be more common in bipolar I and II disorders than in unipolar depression, to be exacerbated by antidepressants and to have a correlation with a bipolar family history loading[4, 23, 72-76]. As a

result, this summary measure targets the presence of soft bipolarity in a sample of outpatients at low risk per se of bipolar illness.

Limitations

One of the main limitations of this study is that we were unable to include all putative predictors of "bipolarity," such as family history of bipolar disorder, in the summary measure. Moreover, although we considered some psychopathological dimensions such as psychoticism, interpersonal sensitivity/rejection avoidance, and irritability/anger/hostility, many other personality traits or lifestyle aspects, such as neuroticism, introversion or extraversion, proneness to anxiety, distinct affective temperaments, number of divorces, sentimental turmoil, economic, geographical instability etc., have been claimed to discriminate unipolar from bipolar depressed subjects[77, 78], but were not available in this dataset.

Also, the summary score we propose assigns an equal weight to each characteristic assessed. We chose this approach because, to the best of our knowledge, there is no data suggesting the relative importance and individual value of non-manic bipolarity markers. Also, because our sample consisted only of outpatients treated with fluoxetine or

placebo, it is unclear if our findings are generalizable to other more severe population of patients needing hospitalization or receiving different medications.

Conclusions

Mood disorders are highly heterogeneous in their phenotypic expression and clinical course of illness[79-81]. Because there are no pathognomonic characteristics of bipolar compared to unipolar depression, it is unlikely that only one symptom, cluster of symptoms, or course specifier can really help the clinician to make a differential diagnosis[82]. Our results suggest that a summary measure of bipolar spectrum features has some predictive validity in terms of recurrences. However, these results do not support the often cited notion that treatment-resistant depression is likely to be bipolar depression. Replication will be necessary in order to extend and generalize our results.

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Table 1. Clinical characteristics included in the summary measure

	N	%
Early onset (age ≤ 21 years)	224	35.6
Recurrent (> 1 episode)	222	35.2
Atypical features	183	29.0
Irritability/hostility/anger	258	41.0
Psychoticism/Paranoid Ideation	238	37.8
Thoughts of suicide	351	55.7
Psychomotor retardation	135	21.4
Anxiety/Bulimia[1]	55	8.7
Alcohol/Substance Abuse/Dependence[2]	148	23.5
Interpersonal sensitivity/rejection avoidance	295	46.8

[1] ≥ 2 current or lifetime disorders in comorbidity among: Panic Disorder, Social Phobia, Obsessive-Compulsive Disorder, Post-Traumatic Stress Disorder, Bulimia

[2] ≥ 1 lifetime alcohol/substance abuse/dependence disorders (study protocol did not allow the inclusion of subjects with current alcohol/substance abuse/dependence comorbidity)

Table 2. Demographic and Baseline Characteristics

			Low Index		High Index			
Characteristic	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	$\chi 2$/ t	p
Sex								
Female	341	54.1	229	51.1	112	62.2	6.25	0.01
Age	37.36	11.44	38.44	11.55	34.70	10.72	3.74	<0.001
Years of education	14.67	2.59	14.79	2.54	14.36	2.67	1.88	0.06
Severity of depression: baseline	17.44	5.13	17.02	4.91	18.36	5.49	2.87	0.004
Severity of depression: time of randomization	7.30	5.68	7.20	5.49	7.52	6.08	0.50	0.62
Race								
Caucasian	469	74.4	332	74.3	137	76.1	0.23	0.6
Marital status								
Single	371	58.9	249	55.8	122	67.8	7.58	0.006
Employment status								
Full time	292	46.3	212	47.6	80	44.7	0.45	0.5

Figure 1. Survival Curve of Time to Remission adjusted for baseline depression severity. Low vs High Index Scores.

Hazard ratio = 1.12 (95% CI = 0.86-1.46, p = 0.39)
Median Low Index = 6.0 (IQR = 10.0-4.0)
Median High Index = 6.0 (IQR = 10.0-3.0)

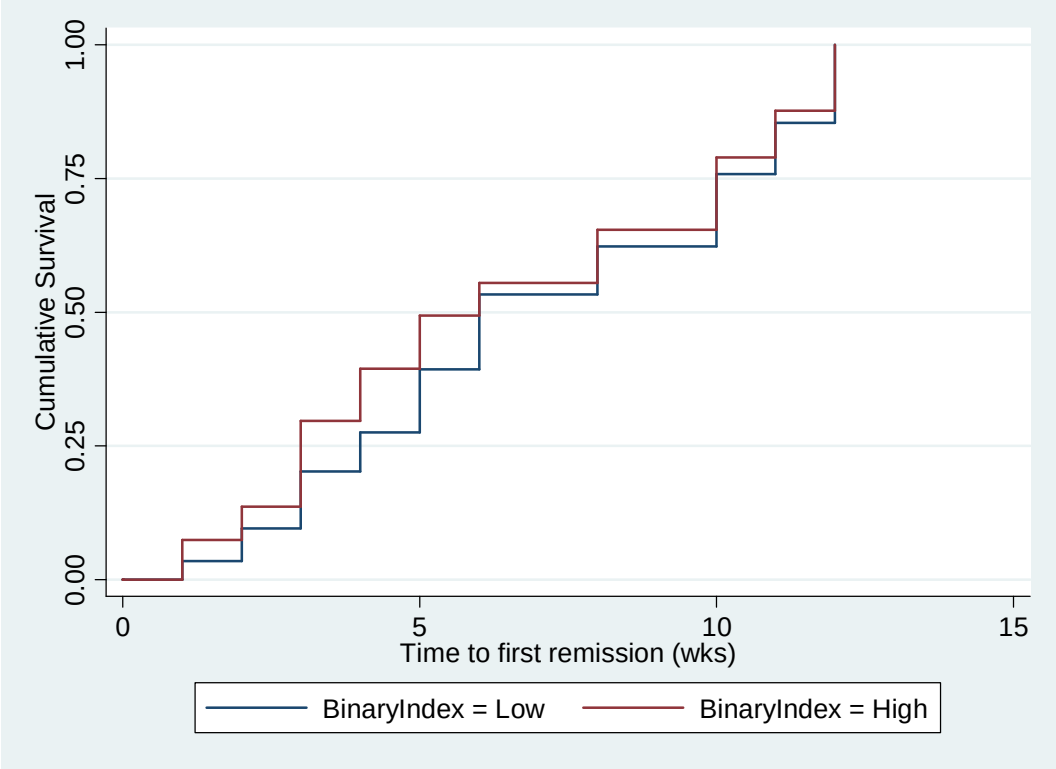

Figure 2. Survival Curve of Time to Recurrence adjusted for depression severity at time of randomization. Low vs High Index Scores.

Hazard ratio = 1.58 (95% CI = 1.09-2.28);
p = 0.016
Median Low Index = 52.0 (IQR = 6- NC)
Median High Index = 12.0 (IQR = 4-NC)