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# Association Between Bipolar Spectrum Features and Treatment Outcomes in Outpatients With Major Depressive Disorder

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## Abstract

**Context—**It has been suggested that patients with major depressive disorder (MDD) who display pretreatment features suggestive of bipolar disorder or bipolar spectrum features might have poorer treatment outcomes.

**Objective—**To assess the association between bipolar spectrum features and antidepressant treatment outcome in MDD.

**Design—**Open treatment followed by sequential randomized controlled trials.

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**Setting—**Primary and specialty psychiatric outpatient centers in the United States.

**Participants—**Male and female outpatients aged 18 to 75 years with a *DSM-IV* diagnosis of nonpsychotic MDD who participated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.

**Interventions—**Open treatment with citalopram followed by up to 3 sequential next-step treatments.

**Main Outcome Measures—**Number of treatment levels required to reach protocol-defined remission, as well as failure to return for the postbaseline visit, loss to follow-up, and psychiatric adverse events. For this secondary analysis, putative bipolar spectrum features, including items on the mania and psychosis subscales of the Psychiatric Diagnosis Screening Questionnaire, were examined for association with treatment outcomes.

**Results—**Of the 4041 subjects who entered the study, 1198 (30.0%) endorsed at least 1 item on the psychosis scale and 1524 (38.1%) described at least 1 recent manic-like/hypomaniclike symptom. Irritability and psychotic-like symptoms at entry were significantly associated with poorer outcomes across up to 4 treatment levels, as were shorter episodes and some neurovegetative symptoms of depression. However, other indicators of bipolar diathesis including recent maniclike symptoms and family history of bipolar disorder as well as summary measures of bipolar spectrum features were not associated with treatment resistance.

**Conclusion—**Self-reported psychoticlike symptoms were common in a community sample of outpatients with MDD and strongly associated with poorer outcomes. Overall, the data do not support the hypothesis that unrecognized bipolar spectrum illness contributes substantially to antidepressant treatment resistance.

The distinction between major depressive disorder (MDD) and bipolar disorder remains a challenging clinical problem when individuals present with a major depressive episode.[1–3] A number of illness features have been proposed to indicate risk of bipolar disorder in this setting, including earlier age of illness onset,[4–7] greater number of depressive recurrences or briefer episodes,[4,6,8,9] family history of bipolar disorder,[6,9–11] and aspects of temperament such as hyperthymia and cyclothymia.[12–15] Symptomatic differences have also been proposed, among them presence of irritability or anger,[16–19] presence of psychotic symptoms,[10,11,20–26] suicidality,[6,25] and atypical neurovegetative symptoms[7,23,27–29] including psychomotor agitation or slowing.[10,30,31] Moreover, even in individuals who do not meet full syndromal criteria for bipolar I or II disorder, it has been suggested that these illness features may be markers for an underlying bipolar diathesis or bipolar spectrum illness.[2,32]

The identification of individuals at risk for bipolar disorder is of more than academic importance, as treatment may be markedly different; in particular, antide-pressants have been suggested to exacerbate the illness course of at least a subset of bipolar individuals.[33–37] Indeed, review articles and continuing medical education programs frequently assert that unrecognized bipolarity is a substantial contributor to apparent treatment-resistant MDD. However, this hypothesis has rarely been tested directly.[38–40] In one of the few empirical investigations, in a cohort of 61 patients previously diagnosed with treatment-resistant MDD seen in a specialty clinic, nearly two-thirds were ultimately re-diagnosed with bipolar disorder.[41] On the other hand, after a decade of articles suggesting underrecognition of bipolar disorder, typically relying on screening tools[42] with limited specificity, it has also been suggested that bipolar disorder may now be overdiagnosed or inappropriately diagnosed.[43] Thus, an unanswered question of substantial clinical importance is whether illness features that may indicate bipolar liability have predictive validity in generalizable clinical populations that present with major depression.

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The Sequential Treatment Alternatives to Relieve Depression study (STAR*D) presents a unique opportunity to address this question. The STAR*D study was an effectiveness study of MDD conducted in both primary and specialty care settings and designed to closely mimic clinical practice.[44] The study's design, which emphasized generalizability to US clinical populations, includes several key features that allow it to estimate predictive validity for bipolar spectrum features. First, reflective of clinical practice, it did not include a structured assessment for bipolar disorder or psychosis. Thus, while individuals who described a prior manic episode or current psychotic symptoms at a screening interview would be excluded by the protocol, if bipolar disorder is as underrecognized as has been suggested,[42] most such patients would not have been screened out. Second, for many features of illness course, the STAR*D study relied on unstructured assessments rather than research instruments such as the Structured Clinical Interview for *DSM* Disorders,[45] again resembling standard clinical practice. Assessments included most, though not all, commonly described indicators of bipolar liability.[2,46] Finally, and most importantly, the STAR*D study examined up to 4 prospective treatment trials, yielding the largest and most systematically defined treatment-resistance cohort to date.

Taken together, the STAR*D study provides an opportunity to examine in a large, ecologically valid cohort the potential effect of unrecognized bipolar disorder or bipolar spectrum features that are routinely assessed in outpatient practices rather than research settings. Specifically, this study examines the association between putative bipolar spectrum features, individually and combined, and antidepressant treatment outcomes.

## METHODS

The STAR*D multicenter trial determined prospectively which of several treatments are most effective in treating participants with nonpsychotic MDD who do not remit with or tolerate first-line treatment with the selective serotonin reuptake inhibitor citalopram. The methods of the STAR*D study are detailed elsewhere[47] and are summarized below.

### STUDY ORGANIZATION

The STAR*D study was carried out by 14 regional centers across the United States, each of which oversaw implementation of the protocol at 2 to 4 clinical sites. Of the 41 clinical sites, 18 were primary care settings and 23 were psychiatric care settings.

Research outcomes were collected by telephone interviews conducted by a small team of trained research outcome assessors who were masked to treatment and by telephone-based interactive voice response. Research outcome assessors received extensive training in the administration of efficacy measures, with interrater reliability assessed periodically.

### STUDY POPULATION

The STAR*D study used broad inclusion and minimal exclusion criteria to ensure a representative sample. The study enrolled male and female outpatients aged 18 to 75 years with a *DSM-IV* diagnosis of nonpsychotic MDD and a baseline score of 14 or greater on the 17-item Hamilton Rating Scale for Depression (HRSD-17)[48] and for whom the treating clinician had determined that outpatient antidepressant treatment was safe and appropriate. Exclusion criteria included lifetime diagnosis of MDD with psychotic features, schizophrenia, schizoaffective disorder, or bipolar disorder I, II, or not otherwise specified based on clinical assessment and self-report (but not self-report questionnaires); a well-documented history of nonresponse or intolerability in the current major depressive episode to adequate doses[49] of 1 or more medications given in the first 2 protocol treatment steps; a current primary diagnosis of eating disorder or obsessive-compulsive disorder; presence of

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severe, unstable concurrent psychiatric conditions likely to require hospitalization within 6 months (eg, severe alcohol dependence with recent detoxification admissions); presence of concurrent medical or psychiatric conditions or concomitant medications that contraindicated a protocol treatment; and pregnancy or intent to conceive within the 9 months subsequent to study entry.

By design, the study recruited only individuals who sought treatment at the clinical sites, so no advertising was permitted. Participants were informed of all risks, benefits, and adverse events associated with each study treatment and provided written informed consent prior to study entry. The study protocol was approved by institutional review boards at all participating sites and monitored by an National Institutes of Mental Health Data Safety Monitoring Board.

## ASSESSMENTS AND OUTCOMES

In addition to sociodemographic data, data collected at the initial study visit included number of prior episodes, current episode duration, age at first episode, history of suicide attempts, and family history of bipolar disorder in first-degree relatives. (For family history, subjects were asked individually about parents, siblings, and children; a positive response to any of these was considered a positive family history for the present analysis). To allow assessment to more closely mimic clinical practice, no structured interview such as the Structured Clinical Interview for *DSM* Disorders[45] or Mini-International Neuro-psychiatric Interview[50] was used. To assess concurrent axis I diagnoses, study participants completed a modified version of the Psychiatric Diagnosis Screening Questionnaire (PDSQ)[51,52]; the psychoticlike symptom screen, which assesses the prior 2 weeks, and the maniclike symptom screen, which assess the prior 6 months, were used in the present analysis. The psy-choticlike symptom screen includes 6 yes/no questions about beliefs of being spied on, plotted against, having special powers, being controlled, or events that others said did not occur, as well as hearing voices or seeing things. Mood congruence was not assessed. In a validation study of approximately 1300 outpatients, sensitivity was 74% and specificity was 74% for psychosis if at least 1 item was endorsed; specificity increased to 89% with 2 items and 96% with 3.[53]

The maniclike symptom screen comprises 6 yes/no questions about elevated mood, extreme self-confidence, decreased need for sleep, talkativeness, new projects, and impulsive activities. This subscale was shown to have only modest correlation (0.51) with another self-report inventory of mania[54] and lower test-retest reliability than other subscales,[52] so sensitivity and specificity were not estimated subsequently.[53] Still, as the only systematic measure of maniclike symptoms and in light of the face validity of the individual items themselves, which resemble those incorporated in structured interviews, this measure was retained for analysis. Results of STAR*D analyses using the other PDSQ subscales have been described elsewhere.[55]

At the initial visit, the study site clinical research coordinator reviewed inclusion and exclusion criteria and completed the HRSD-17 and the 16-item Quick Inventory of Depressive Symptomatology (QIDS-C16).[56] The clinical research coordinator was not required to review the PDSQ results.

Within 72 hours of the baseline visit, a research outcomes assessor blinded to participant treatment status conducted a telephone interview with study participants to complete a second baseline HRSD-17 score as well as the 30-item Inventory of Depressive Symptamology–Clinician Rated[56,57]; the HRSD-17 was repeated by a research outcomes assessor following each study visit. Subjects also completed the self-report form of the brief Inventory of Depressive Symptamology (QIDS-SR) at baseline and each subsequent study

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visit; this was used as the secondary outcome measure in the STAR*D study. Primary study outcomes defined by protocol included 2 definitions of remission based on self-report (QIDS-SR score ≤5) and assessment by a blinded rater (HRSD-17 score ≤7). As the former definition was available for more subjects and has been considered the primary outcome in prior STAR*D analyses, the present investigation focused on QIDS-SR–defined outcomes. As in prior articles, irritability[58] was defined according to Inventory of Depressive Symptomatology item at study entry.

## INTERVENTIONS

All patients were treated with citalopram at level 1, with a goal of achieving symptomatic remission.[44] Dosing was directed by a treatment manual (www.star-d.org), which suggests a starting dose of 20 mg/d of citalopram, increased to 40 mg/d by weeks 2 to 4 and 60 mg/d by weeks 4 to 6. Adjustments were allowed to minimize adverse effects, maximize safety, and optimize the likelihood of therapeutic benefit for each patient.

For those individuals entering level 2, treatment was randomized to either citalopram augmentation with buspirone or bupro-pion, or switch to sertraline, venlafaxine, or bupropion. (A small subset of individuals received cognitive therapy in addition to or in lieu of citalopram following level 1.) Treatments at level 3 included switching to nortriptyline or mirtazapine or augmentation (of current antidepressant) with lithium or thyroid hormone. Treatments at level 4 included switching to tranylcypromine or the combination of mirtazapine and venlafaxine.

At each level, treatment visits occurred at 0, 2, 4, 6, 9, and 12 weeks; an optional 14-week visit could be added if needed. After up to 14 weeks of treatment, all subjects who did not achieve remission were encouraged to enter the subsequent level. Patients could also exit the current level prior to 12 weeks and enter the next level if they experienced intolerable adverse effects, could not reach an optimal antidepressant dose because of adverse effects, or continued to have significant symptoms defined as a QIDS-C16 score of 9 or greater after at least 9 weeks at the maximal tolerable dose. While both remitters and responders could enter the 12-month naturalistic follow-up, the latter group was also encouraged to enter next-step treatment with a goal of achieving remission.

## STATISTICAL ANALYSIS

The variables to be considered as putative bipolar spectrum features were selected by consensus among the authors by intersecting those implicated in recent systematic reviews[46] with the available data in the STAR* D study. They include aspects of course: episode duration, age at onset, frequency of recurrence; family history of bipolar disorder; and symptoms at study entry: irritability, psychomotor symptoms, hypersomnia, and hyperphagia, as well as manialike and psychosislike subscale items from the PDSQ. To address nonnormal distributions and reflect published criteria for bipolar spectrum features, continuous variables including episode duration and recurrences were dichotomized to indicate episode duration of less than or equal to 3 months and 3 or more prior episodes. In the absence of agreement in the literature on the optimal cutoff for onset age, this variable was considered as a continuous measure, then dichotomized at 25 years of age for consistency with the criteria of Ghaemi and Goodwin.[2] The count of PDSQ psy-chosislike and manialike subscale items was dichotomized in primary analyses to indicate presence or absence of at least 1 feature of each, as the distribution of scores was highly skewed to the right. That is, those in the group with psychosis endorsed at least 1 of the PDSQ items used to screen for possible psychotic symptoms within 2 weeks of study entry. For exploratory purposes, associations with scores of 2 or more and 3 or more on each subscale were also examined.

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Three approaches were used to examine the hypothesis that bipolar spectrum features are associated with poorer treatment outcomes in individuals diagnosed with MDD. First, the features were examined individually for association with outcome. Second, they were examined in combination using the definition of bipolar spectrum disorder described by Ghaemi and colleagues.[2] This definition prioritizes family history of bipolar disorder in a first-degree relative or history of antidepressant-induced mania or hypomania. Additional criteria include hy-perthymic personality, more than 3 prior major depressive episodes, brief major depressive episodes (<3 months on average), atypical depressive symptoms by *DSM-IV*, psychotic symptoms, onset of depression before 25 years of age, postpartum depression, absence of sustained antidepressant effect, and treatment resistance. From these, we selected the criteria that do not reflect antidepressant response (as that represented the hypothesis being tested here) and which were not collected, omitting history of antidepressant-induced mania, lack of sustained an-tidepressant response, and treatment resistance; hyperthymia and postpartum depression were also omitted. Syndromal bipolar spectrum disorder was thus defined as family history of bipolar disorder with at least 1 other putative feature or 3 of 5 putative features in the absence of family history.

To examine the association between individual bipolar spectrum features, or syndromal bipolar spectrum (as well as potential sociodemographic and clinical confounding variables), and longitudinal outcomes, survival methodology was used with results right-censored at study exit or remission; the 369 subjects with no postbaseline visits were excluded, yielding a modified intent-to-treat cohort (n=3672). Because the primary outcome of interest was number of trials required for remission rather than within-level time to remission, the time variable was the level number. In other words, primary analysis examined “levels (or interventions) to remit” rather than “days to remit,” considering subjects with at least 1 postbaseline visit (ie, a modified intent-to-treat approach). Sensitivity analysis examining overall days, rather than levels, to achieve remission yielded similar results and are presented in eTable 1 (http://www.archgenpsychiatry.com). Cox regression was used to examine the association between bipolar spectrum features and outcome, first adjusted for baseline depression severity alone (as measured by HRSD-17) and then adjusted for all potential sociodemographic and clinical confounding variables. Alternate approaches to addressing confounding, including use of stepwise backward-elimination techniques, yielded essentially identical results in all cases. Given the modest sample sizes in individual treatment arms, particularly at level 3 and higher, treatment × predictor interactions were not considered. For putative proxy markers of poor outcome, including absence of postbaseline visit, loss to follow-up, and psychiatric significant adverse events including suicide attempt and hospitalization, multiple logistic regression was used, with adjustment for baseline depression severity and then for additional potential confounding variables.

Rather than arbitrarily weighting the individual features, a third set of analyses attempted to define weights of bipolar spectrum features empirically. This approach fitted a structural equation model (SEM) with bipolarity as a latent (ie, not directly observed) variable indicated indirectly by proxy measures including age at onset, recurrence, atypical neurovegetative and psychomotor symptoms, psychoticlike symptoms in the 2 weeks prior to study entry, maniclike symptoms in the 6 months prior to study entry, irritability, and family history of bipolar disorder (eFigure 1). Initially, a measurement model was fitted as a confirmatory factor analysis in which all indicators load on a single common factor reflecting latent bipolarity. Treatment resistance was then modeled as a discrete time survival of unremitting depression in subsequent levels of the treatment trial with censoring of missing values. To reflect the hypothesis that indicators contribute to treatment resistance as a function of bipolar disposition, treatment resistance was regressed on the latent bipolarity with no direct effects of indicators on treatment outcome. The SEM was fitted using maximum likelihood with the EM algorithm and up to 10 000 iterations. This method

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converges on a solution that maximizes the explanation of covariance between observed variables and allows different weighing of indicators on the latent bipolarity to explain treatment resistance. The SEM approach was also applied to examine the association between latent bipolarity and study discontinuation following baseline visit, subsequent loss to follow-up, or psychiatric serious adverse events.

Univariate analyses used Stata 10.0 (Statacorp, College Station, Texas). The SEM analyses used Mplus 5.21.[59]

## RESULTS

Of 4173 subjects consented, 132 were excluded following consent based on the clinical research coordinator evaluation, including 23 diagnosed with bipolar disorder and 8 with a history of psychotic symptoms. The so-ciodemographic and general clinical features of the remaining 4041 have been described elsewhere.[60] Table 1 summarizes the distribution of putative bipolar spectrum features for all subjects. Notably, 1524 of 3999 participants (38.1%) endorsed at least 1 maniclike/hypomaniclike symptom on the PDSQ in the prior 6 months (PDSQ was not completed for 42 subjects). On the PDSQ psychosislike screen, 1198 of 3999 participants (30.0%) endorsed at least 1 symptom in the prior 2 weeks (eTable 2 lists the proportion of subjects who endorsed individual psychoticlike screen items). In all, 650 participants (16.2%) described having both manic-like and psychoticlike symptoms.

The first set of analyses examined the association between individual features, or sets of features, and treatment resistance. Possible confounding sociodemo-graphic and clinical features were examined in univariate models for association with outcome (eTable 3); greater depression severity, self-reported race other than white, being unmarried, having public insurance, not graduating from high school, and comorbid panic disorder (by PDSQ) were found to be associated with treatment-resistant MDD, and analyses of bipolar spectrum features were adjusted for them.

Table 2 summarizes hazard ratios for remission of individual putative bipolar spectrum features. After adjustment for potential confounders from eTable 3, presence of psychoticlike symptoms, irritability, psychomotor symptoms, and hyperphagia were significantly associated with nonremission across subsequent therapeutic trials, while family history of bipolar disorder and presence of manic symptoms were not significantly associated with outcome. Brief episode duration, but not greater number of episodes, was associated with better outcome.

Bipolar spectrum criteria using the standards of Ghaemi and Goodwin[2] could be evaluated in 3166 subjects; the remainder could not be scored because of indeterminate number of past episodes or insufficient data to define atypical depression. Of those who could be evaluated, 870 of 3166 participants (27.6%) met the a priori criteria for bipolar spectrum disorder. No significant association with nonremis-sion was identified (Table 2) with or without adjustment for potential confounding variables.

We then used SEM models to examine the relationships between indicators of bipolarity and the effect of a latent bipolar spectrum variable on remission. The putative indicators of bipolarity were generally only weakly correlated (average $\rho$=0.08; eTable 4). Reflecting the relatively weak correlations, a common factor explained a large proportion of covariance (0.74) but only a small proportion of variance (0.21) of the 8 indicators, and the measurement confirmatory analysis model had suboptimal fit (eTable 5). The measurement model suggested high loading of age at onset and recurrence but low loadings from more specific indicators of bipolar diathesis (eTable 4, eTable 6, and eTable 5 for details of model structure and fit). These results suggest that the concept of latent bipolarity defined by the 8

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indicators has low internal consistency (Cron-bach α=.14). That is, they suggest that the previously proposed collection of indicators is unlikely to reflect a single phenomenon. However, even if the commonality between the indicators is small, it may still be predictive of clinically relevant outcomes. Therefore, a survival SEM examined if latent bipolarity predicted resistance across the 4 courses of treatment in STAR*D (eFigure 1). While some individual clinical features might independently predict poorer outcome, these models allowed an examination of the effect of this putative category on outcome. The best fitting structural equation model (eTables 4–6 and eFigure 2) showed inconsistent loading of indicators on the latent bipolarity variable and no significant relationship between latent bipolarity and treatment resistance ($z$=1.015; $P$=.31). Psychoticlike symptoms exhibited the strongest loading on latent bipolarity, but other indicators including family history of bipolar disorder loaded nonsignifi-cantly, reflecting the weak and inconsistent correlations between the indicators. The nonsignificant relationship between latent bipolarity and treatment outcome further supports the lack of consistent association between the grouping of indicators and treatment outcome observed in the univariate analyses.

In addition to treatment resistance, unrecognized bipolar spectrum illness has been suggested to contribute to adverse effects among individuals exposed to antidepres-sants. Therefore, the second set of analyses examined adverse outcomes associated with exposure of bipolar patients to antidepressants. With citalopram treatment, 2 subjects developed manic episodes, 1 at day 36 and 1 at day 41 of treatment; 2 others developed hallucinations (one, command auditory hallucinations at or shortly after study entry; the other, unspecified hallucinations at day 26). Of these 4, 1 had a positive family history of bipolar disorder (and met criteria for bipolar spectrum disorder), 2 reported at least 1 manic symptom, and 1 reported at least 1 psychotic symptom. One of the 4 met Ghaemi and Good-win[2] criteria for bipolar spectrum illness.

Additional outcomes that might serve as proxies for an-tidepressant-associated adverse events included rapid study discontinuation (failure to return for a postbaseline visit), early discontinuation with loss to follow-up, and serious adverse events including psychiatric hospitalization or suicide attempt. For each of these outcomes, we first examined sociodemographic or clinical features that might confound associations with that outcome (eTable 7), then adjusted for these variables in subsequent analyses (Table 3). Only onset of illness at or after 25 years of age was associated with risk of failure to return for a postbase-line visit (Table 3), while other putative bipolar spectrum features and meeting criteria for bipolar spectrum illness were not. For study discontinuation with loss to follow-up, *DSM-IV* atypical depression and greater irritability and/or agitation on the Inventory of Depressive Symptamology were associated with greater risk, while briefer episode duration was associated with decreased risk. Again, no association with other individual illness features or bipolar spectrum illness was identified. Finally, greater risk of a significant adverse event was associated with briefer episode duration and 3 or more past episodes but not with any other variables examined.

When the latent bipolarity variable was examined for association with these putative proxy outcomes in level 1 of the STAR*D study in SEM models (eFigure 3, eFigure 4, and eFigure 5), no evidence of association was observed for failure to return after postbaseline visit (β=−.042; standard error [SE]=0.038; $P$=.27) or early discontinuation (β=.055; SE=0.066; $P$=.41). However, significant association was identified with psychiatric serious adverse effects (β=.297; SE=0.077; $P$<.001).

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## COMMENT

Our results indicate that putative bipolar spectrum features are common in this general clinical population presenting for treatment of MDD. In particular, the substantial proportion of individuals with at least 1 self-reported recent psychoticlike or maniclike PDSQ screening item suggests that the STAR*D cohort reflects routine practice, where individual symptoms may not be routinely recognized or considered to be of sufficient clinical importance to guide treatment selection.

It must be emphasized that the presence of subjects who endorsed individual psychoticlike or maniclike symptoms does not imply that this study of nonpsychotic individuals with MDD enrolled persons with *DSM-IV*–defined bipolar disorder or psychotic depression. Rather, these symptoms may be better understood as features that, if recognized, might prompt consideration of a bipolar spectrum illness in some clinical contexts. For psychosis, a large validation study suggested specificity was 89% when 2 items were endorsed and 96% when 3 or more items were endorsed.[53] The maniclike subscale is more problematic from a psychometric perspective.[51,53] Still, it measures symptoms commonly assessed in clinical practice to screen for past or current manic/mixed episodes, and thus was retained for analysis based on face validity. Nonetheless, failure to identify association with outcome must be interpreted with this limitation in mind.

Analyses of remission suggest that the presence of even a single self-reported recent psychoticlike symptom is associated with poorer antidepressant response across multiple treatment levels. While the presence of a single symptom is not diagnostic for a psychotic disorder, such symptoms appear to have strong predictive validity, supporting prior studies of poorer outcomes with (syndromal) psychotic depression. In particular, our results are consistent with data from the Epidemiologic Catchment Area study that found more chronicity and recurrence risk in psychotic MDD[61] and similar results in a 10-year follow-up from the National Institutes of Mental Health Collaborative Depression Study.[62]

On the other hand, several indicators consistently associated with bipolar disposition in the literature, including history of manic symptoms and family history of bipolar disorder,[46] were not associated with outcome of treatment with antidepressants in the STAR*D study. Briefer episode duration, suggested to represent a risk marker for bipolarity, was associated with greater likelihood of remission. Moreover, even if some individual symptoms suggested to be indicative of a bipolar diathesis are associated with poorer outcome, it does not necessarily follow that the diathesis itself is associated with poorer outcome. (In the same fashion, even if fever is associated with poorer outcome in hospitalized patients and sometimes indicates pneumonia, it would not necessarily follow that pneumonia mediates most poor outcomes). We adopted 2 complementary approaches to examine this bipolar diathesis, one based on previously proposed criteria that arbitrarily weigh symptoms, the second based on empirically deriving a latent variable. Meeting criteria for bipolar spectrum illness was not associated with any differential outcome, whether in terms of remission or adverse events. In general, the results of SEM models also strongly suggest that individual symptoms or risk factors explain these poorer outcomes better than a latent bipolar spectrum factor.

The one exception was psychiatric serious adverse events, in which a significant association with risk was identified in the SEM model. Here, inspection of factor loading is informative, indicating strong effects of earlier onset and recurrence (eFigure 5). Thus, the most parsimonious interpretation of this finding, apart from type I error, is simply that recurrent and early-onset MDD may indicate greater risk of adverse outcomes.

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The inconsistent prediction of outcomes of interest by the various previously proposed indicators of latent bipolarity raises the question of whether these indicators tap into a uniform concept. Our data suggest that this is unlikely. The latent bipolarity variable exhibited poor internal consistency, reflecting the fact that the putative bipolar spectrum variables are not highly correlated. Indeed, based on the consideration of factor loading, it might be argued that this variable poorly captures the core bipolar spectrum features such as family history. Of course, this argument could be made about any arbitrary weighting of bipolar spectrum features, given the lack of clear agreement on the relative importance of such features. This was the primary rationale for the complementary analysis examining a definition of bipolar spectrum illness based specifically on previously described criteria.

In addition to demonstrating the predictive validity of self-reported symptoms on psychosislike symptom screening, 3 broader conclusions follow from these analyses. First, they suggest that the prevalence of bipolar disorder in otherwise-unselected populations of individuals who had a major depressive episode may be well below the 25% to 50% estimated in studies that use a nonspe-cific measure of bipolarity such as the Mood Disorders Questionnaire.[42] If a large subset of patients had actually been misdiagnosed, as these studies would suggest, we would have anticipated substantially poorer outcomes, either in terms of remission or adverse events, in this group at risk for bipolar disorder. We observed none of these, despite a large cohort with excellent statistical power to detect such effects.

Second, they contradict the often-cited notion that a large proportion of apparently treatment-resistant MDD is actually bipolar disorder or bipolar spectrum illness.[41] Were this the case, bipolar loading (whether in terms of a latent variable or a categorical definition such as that proposed by Ghaemi and Goodwin[2]) should predict poorer outcome across levels, beyond the effect of individual clinical features such as irritability. This was not observed during up to 1 year of sequential treatment. Thus, while treatment-resistant MDD should certainly prompt reconsideration of the primary diagnosis and comorbidity, it does not appear to be the case that many or most of these patients actually have unrecognized bipolar disorder in a typical outpatient setting.

Third, our findings suggest that the bipolar spectrum, defined by a broad range of indicators derived from a comprehensive literature review, has modest predictive validity. This does not imply that the bipolar spectrum concept is not a useful one, nor that it might not be validated by other means such as genetic investigation.[63] However, our results provide little support for the predictive validity of bipolar spectrum illness in a gen-eralizable population of treatment-seeking adult patients diagnosed with MDD.

Several limitations bear consideration in interpreting these results. Despite intensive efforts to design a study that closely mimics clinical practice, it can be argued that the requirement for necessary aspects of human subjects research (informed consent, rating scales) yields a study population that might not generalize well. Supporting the greater generalizability of this cohort compared with most clinical trials, most patients in the STAR*D study would have been excluded from MDD efficacy studies.[64]

In addition, while the STAR*D study did not include systematic assessment for bipolar disorder, subjects with overt features of bipolar disorder were excluded per protocol. Such exclusion probably mimics what transpires with depressed patients in general practice: even clinicians who do not screen for bipolar disorder would be likely to consider the diagnosis when a patient reports a previous diagnosis of bipolar I disorder or a prior manic episode. In general, the subtler presentations of bipolar II disorder could be less likely to have been detected at entry into the STAR*D study. Supporting this assertion, many patients self-

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reported recent hypomaniclike or psy-choticlike symptoms but were not excluded. Nonetheless, the deliberate exclusion of overtly bipolar patients could have limited our power to detect effects on outcome. In a similar fashion, as STAR*D did not include formal measures of manic symptomatology, it is possible that some patients who developed such symptoms would be unrecognized. However, if such symptoms did not meaningfully affect detectable clinical outcomes, their clinical importance is likely to be modest in general outpatient clinical populations.

Finally, some of the measures incorporated here, such as onset age, family history, and prior course, were assessed using simple instruments (ie, patient report) rather than the more detailed research measures used in, for example, some genetic investigations.[65] While their lack of precision may bias results toward the null, we note that, for some longitudinal history measures, significant associations with outcome were still detected. More importantly, these assessments—as with many of the PDSQ questions—mimic real-world clinical practice, and therefore provide a useful measure of how standard clinical assessment may or may not be useful in predicting outcome.

We also note that the STAR*D study was not designed to investigate bipolar spectrum features and, in particular, does not include measures of temperament or personality, which others have suggested are indicative of a bipolar diathesis. These include, for example, hyperthymic and cyclothymic temperament[12–15] as well as borderline personality disorder[66]; in particular, rapid affective shift is not examined in the data available to us. Still, most of the other clinical features suggested in multiple studies cited as criteria for bipolar spectrum illness[2] and highlighted by a consensus panel[46] could be examined in the STAR*D data set. In light of these strengths and limitations, the present results are likely to generalize to routine psychiatric care and general practice but may not be entirely consistent with experience in highly specialized mood disorder clinics using more intensive assessment.

Considered as a whole, our results cast doubt on the frequent assertion that unrecognized bipolar disorder is widespread in clinical practice and particularly in treatment-resistant MDD. Screening for bipolar disorder among psychiatric patients remains important, as does considering individual risk factors such as family history or age at onset.[46] Still, our findings indicate that, in most individuals presenting with a major depressive episode without a prior manic or hypomanic episode, unrecognized bipolarity does not appear to be a major determinant of treatment resistance.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Table 1

Prevalence of Possible Bipolar Spectrum Features in the STAR*D Cohort

| Feature | Present, No. (%) | Assessed, No.[a] |
|---|---|---|
| Family history of bipolar disorder | 351 (8.8) | 4001 |
| Episode duration ≤3 mo | 872 (21.6) | 4040 |
| ≥3 Prior episodes | 1275 (36.5) | 3495 |
| Onset before 25 y of age | 2315 (57.9) | 3996 |
| Atypical depression (*DSM-IV* diagnosis) | 635 (17.0) | 3740 |
| Manialike symptoms, No. | | |
| ≥1 | 1524 (38.1) | 3999 |
| ≥2 | 821 (20.5) | 3999 |
| ≥3 | 444 (11.1) | 3999 |
| Psychosislike symptoms, No. | | |
| ≥1 | 1198 (30.0) | 3999 |
| ≥2 | 526 (13.2) | 3999 |
| ≥3 | 217 (5.4) | 3999 |
| Bipolar spectrum illness[b] | 870 (27.5) | 3166 |
| **Feature** | **Mean (SD)** | **No.[a]** |
| IDS | | |
| Irritability | 1.33 (0.86) | 3743 |
| Slowing | 0.70 (0.59) | 3744 |
| Agitation | 0.87 (0.79) | 3743 |
| Hypersomnia | 0.44 (0.87) | 3744 |
| Increased appetite | 0.46 (0.94) | 3743 |
| Onset age, y | 25.50 (14.40) | 3996 |
| PDSQ | | |
| Manialike score | 0.80 (1.31) | 3999 |
| Psychosislike score | 0.52 (0.97) | 3999 |

Abbreviations: IDS, Inventory of Depressive Symptoms; PDSQ, Psychiatric Diagnosis Screening Questionnaire; STAR*D, Sequential Treatment Alternatives to Relieve Depression study.

[a] Numbers vary because not all assessments were completed for all subjects.

[b] Bipolar spectrum defined by Ghaemi and Goodwin criteria[2]; see text for details.

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## Table 2

Association Between Individual Bipolar Spectrum Features and Hazard for Remission Across Levels in STAR*D

| | HR (95% CI) | |
|---|---|---|
| **Feature** | **Crude** | **Adjusted** |
| Family history of bipolar disorder | 0.98 (0.84–1.15) | 0.96 (0.82–1.12) |
| Episode duration ≤3 mo | 1.11 (1.01–1.23)[a] | 1.10 (1.00–1.22)[a] |
| ≥3 Prior episodes | 0.96 (0.88–1.06) | 0.95 (0.86–1.04) |
| Onset before 25 y of age | 0.99 (0.91–1.08) | 1.00 (0.91–1.09) |
| Atypical depression (*DSM-IV* diagnosis) | 0.86 (0.76–0.97)[a] | 0.89 (0.79–1.00) |
| Maniclike symptoms, No. | | |
| ≥1 | 0.99 (0.90–1.08) | 1.02 (0.93–1.12) |
| ≥2 | 1.03 (0.93–1.15) | 1.07 (0.96–1.20) |
| ≥3 | 1.08 (0.94–1.24) | 1.13 (0.99–1.30) |
| Psychosislike symptoms, No. | | |
| ≥1 | 0.78 (0.71–0.87)[a] | 0.83 (0.75–0.93)[a] |
| ≥2 | 0.72 (0.61–0.84)[a] | 0.78 (0.66–0.91)[a] |
| ≥3 | 0.79 (0.62–1.00) | 0.88 (0.69–1.13) |
| Bipolar spectrum illness[b] | 0.94 (0.84–1.04) | 0.93 (0.84–1.04) |
| IDS | | |
| Irritability | 0.92 (0.87–0.97)[a] | 0.92 (0.87–0.97)[a] |
| Slowing | 0.88 (0.81–0.95)[a] | 0.90 (0.83–0.97)[a] |
| Agitation | 0.89 (0.84–0.94)[a] | 0.89 (0.84–0.95)[a] |
| Hypersomnia | 0.96 (0.91–1.01) | 0.96 (0.91–1.01) |
| Increased appetite | 0.93 (0.88–0.97)[a] | 0.93 (0.89–0.98)[a] |
| Onset age, y | 1.00 (1.00–1.00) | 1.00 (1.00–1.00) |
| PDSQ | | |
| Manialike score | 1.01 (0.98–1.05) | 1.03 (0.99–1.06) |
| Psychosislike score | 0.87 (0.83–0.92)[a] | 0.90 (0.85–0.96)[a] |

Abbreviations: CI, confidence interval; HR, hazard ratio; IDS, Inventory of Depressive Symptoms; PDSQ, Psychiatric Diagnosis Screening Questionnaire.

[a] Ninety-five percent CI excludes 1.

[b] Bipolar spectrum defined by Ghaemi and Goodwin criteria[2]; see text for details.

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## Table 3

Association Between Individual Bipolar Spectrum Features and Adjusted Risk of Adverse Outcomes Including Early Discontinuation, Loss to Follow-Up, and Psychiatric Significant Adverse Effect

| | OR (95% CI) | | |
|---|---|---|---|
| **Feature** | **Early Discontinuation** | **Loss to Follow-up** | **Adverse Event** |
| Family history of bipolar disorder | 0.67 (0.43–1.06) | 0.76 (0.48–1.19) | 0.91 (0.43–1.93) |
| Episode duration ≤3 mo | 1.21 (0.93–1.57) | 0.69 (0.50–0.95) | 1.78 (1.11–2.86) |
| ≥3 Prior episodes | 0.86 (0.66–1.11) | 0.77 (0.58–1.02) | 1.66 (1.02–2.70) |
| Onset before 25 y of age | 0.75 (0.58–0.97)[a] | 0.85 (0.65–1.13) | 1.16 (0.68–1.98) |
| Atypical depression (*DSM-IV* diagnosis) | 0.84 (0.60–1.18) | 1.61 (1.21–2.15) | 0.82 (0.43–1.55) |
| Maniclike symptoms, No. | | | |
| ≥1 | 1.02 (0.81–1.28) | 1.08 (0.85–1.38) | 0.96 (0.61–1.52) |
| ≥2 | 1.04 (0.80–1.35) | 1.05 (0.79–1.39) | 1.21 (0.73–2.00) |
| ≥3 | 1.15 (0.83–1.58) | 1.06 (0.75–1.51) | 1.06 (0.56–2.00) |
| Psychosislike symptoms, No. | | | |
| ≥1 | 0.99 (0.77–1.27) | 1.19 (0.92–1.54) | 0.87 (0.53–1.41) |
| ≥2 | 1.06 (0.77–1.45) | 1.03 (0.74–1.44) | 0.71 (0.38–1.33) |
| ≥3 | 1.15 (0.75–1.78) | 0.81 (0.49–1.32) | 0.65 (0.27–1.59) |
| Bipolar spectrum illness[b] | 0.90 (0.66–1.23) | 0.95 (0.70–1.29) | 0.98 (0.56–1.72) |
| IDS | | | |
| Irritability | 1.09 (0.94–1.26) | 1.18 (1.02–1.37) | 0.91 (0.68–1.21) |
| Slowing | 0.86 (0.70–1.08) | 1.02 (0.82–1.26) | 1.26 (0.83–1.90) |
| Agitation | 1.05 (0.89–1.25) | 1.23 (1.04–1.45) | 1.11 (0.81–1.51) |
| Hypersomnia | 1.11 (0.97–1.27) | 0.98 (0.85–1.13) | 0.90 (0.67–1.22) |
| Increased appetite | 0.93 (0.81–1.07) | 0.98 (0.86–1.12) | 1.04 (0.81–1.33) |
| Onset age, y | 1.01 (1.00–1.02)[a] | 1.01 (1.00–1.02) | 1.00 (0.98–1.02) |
| PDSQ | | | |
| Manialike score | 1.03 (0.95–1.11) | 1.01 (0.93–1.10) | 1.00 (0.86–1.17) |
| Psychosislike score | 0.99 (0.88–1.11) | 1.03 (0.91–1.15) | 0.89 (0.72–1.11) |
| Latent bipolar variable | 0.59 (0.25–1.36) | 1.82 (0.73–4.54) | 1.38 (0.25–7.52) |

Abbreviations: CI, confidence interval; IDS, Inventory of Depressive Symptoms; OR, odds ratio; PDSQ, Psychiatric Diagnosis Screening Questionnaire.

[a] Ninety-five percent CI excludes 1 (ie, significant at $P<.05$).

[b] Bipolar spectrum defined by Ghaemi and Goodwin criteria[2]; see text for details.