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Irritability is associated with anxiety and greater severity, but not bipolar spectrum features, in major depressive disorder

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Abstract

Objective—Irritability is common during major depressive episodes, but its clinical significance and overlap with symptoms of anxiety or bipolar disorder remains unclear. We examined clinical correlates of irritability in a confirmatory cohort of Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study participants with major depressive disorder (MDD).

Method—Logistic regression was used to identify features associated with presence of irritability on the clinician-rated Inventory of Depressive Symptomatology.

Results—Of 2,307 study participants, 1067(46%) reported irritability at least half the time during the preceding week; they were more likely to be female, to be younger, to experience greater depression severity and anxiety, and to report poorer quality of life, prior suicide attempts, and suicidal ideation. Bipolar spectrum features were not more common among those with irritability.

Conclusion—Irritable depression is not a distinct subtype of MDD, but irritability is associated with greater overall severity, anxiety comorbidity, and suicidality.

Keywords

major depressive disorder; bipolar disorder; diagnosis; irritability; anger; suicide

INTRODUCTION

Irritability and anger during major depressive episodes are absent from standard DSM-IV diagnostic criteria for adults [1,2]. In a previous report on the first 1,500 outpatients to enter the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, an outpatient study of nonpsychotic major depressive disorder (MDD), we found significant irritability in 40% of participants [3]. This was consistent with previous reports describing these symptoms in outpatient populations[4–6]. Such symptoms appear to be associated with greater disease morbidity, reflected in greater overall depression severity and level of anxiety, as well as risk for vascular disease[3,7,8]. Elevated levels of anger, irritability, or hostility have also been repeatedly associated with risk for suicide attempts [3,9–14].

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Recently, irritability during depressive episodes has also been suggested to be a marker for undiagnosed or subthreshold bipolar disorder, or so-called bipolar spectrum illness. [15–18]. Under this theory, putative markers of a bipolar diathesis would be expected to co-occur more often than would be expected by chance…

The STAR*D study offers a unique opportunity to examine the clinical significance of irritability. First, it utilized broad inclusion criteria which allowed psychiatric and medical comorbidity, and did not allow advertisements, so it should be more representative of clinical populations of patients with major depressive disorder than standard randomized, controlled trials[19]. As such, results should be broadly generalizable to clinical practice. Second, it was large enough to allow for examination of two independent cohorts, minimizing the risk of spurious association. The present study was therefore intended to replicate and extend findings from the initial STAR*D cohort [3].

Specifically, we attempted to clarify two clinically important questions using the larger STAR*D confirmatory cohort. First, does irritability represent a meaningful *subtype* of MDD which can be distinguished from other clinical variants of depression, particularly anxious depression [20] and depression of greater severity [3]? Second, are other illness features suggestive of a bipolar diathesis - earlier onset of illness, greater recurrence, family history of bipolar disorder or substance abuse, and atypical depressive symptoms[3,15,16,21–23] – more common among those individuals with irritability, as might be expected if irritability is a marker of bipolar spectrum illness?

Aims of the study

We sought to confirm and extend associations between depression with irritability and other clinical variants of depression, such as atypical or anxious depression, as well as other markers of morbidity. We also examined whether so-called ‘bipolar spectrum’ features were overrepresented among individuals with depression and irritability.

Material and 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 [24] and are summarized below.

Study Organization

The STAR*D study was carried out by 14 Regional Centers (RC’s) across the United States, each of which oversaw implementation of the protocol at two to four 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 (ROAs) masked to treatment, and by telephone-based Interactive Voice Response (IVR). ROAs received extensive training in the administration of efficacy measures, with inter-rater reliability assessed periodically.

Study Population

This report presents data from the final 2,307 participants who entered Level 1 (citalopram) treatment in STAR*D for whom the 30-item Inventory of Depressive Symptomatology – Clinician-Rated (IDS-C_{30})[25,26], which included an assessment of irritability, was completed by the ROAs. The study recruited only individuals who sought treatment at the clinical sites; advertising to recruit participants was not permitted. Participants were

informed of all risks, benefits, and adverse events associated with each study treatment and they provided written informed consent prior to study entry. The study protocol was approved by institutional review boards at all participating sites and monitored by the Data Safety Monitoring Board at NIMH.

STAR*D used broad inclusion and minimal exclusion criteria to ensure a representative sample. The study enrolled male and female outpatients, age 18–75, with a DSM-IV diagnosis of non-psychotic MDD and a baseline score ≥14 on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$)[27], not currently treated with an antidepressant, for whom the treating clinician had determined that outpatient antidepressant treatment was safe and appropriate. Full exclusion criteria have been reported elsewhere [3]. These include a well-documented history of nonresponse or intolerability in the current major depressive episode to adequate doses[28] of one or more medications utilized in the first two protocol treatment steps; lifetime diagnosis of MDD with psychotic features, schizophrenia, schizoaffective disorder, or bipolar disorder; a current primary diagnosis of eating disorder or obsessive-compulsive disorder; presence of severe, unstable concurrent psychiatric conditions likely to require hospitalization within six months (e.g., 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 nine months subsequent to study entry. Individuals with suicidal thoughts or intent at study entry were not specifically excluded, provided outpatient treatment was determined to be safe and appropriate by study clinicians.

Information collected at the initial visit included clinical and demographic data, prior course of illness, current and past substance abuse, prior suicide attempts, family history of MDD or bipolar disorder, current general medical illnesses, and prior history of treatment (both medication and psychotherapy) in the current major depressive episode. Participants completed a modified version of the Psychiatric Diagnosis Screening Questionnaire (PDSQ) [29,30] for assessment of types and degree of concurrent psychiatric symptoms.

The Clinical Research Coordinator (CRC) at the study site completed the $HRSD_{17}$ at baseline, reviewed inclusion/exclusion criteria, and completed the 16-item Quick Inventory of Depressive Symptomatology ($QIDS\text{-}C_{16}$)[26], which is a clinician-rated scale that assesses nine diagnostic symptom domains of MDD. Current general medical conditions (GMCs) were assessed using the 14-item Cumulative Illness Rating Scale (CIRS)[31,32] using a scoring manual to evaluate the severity/morbidity of GMCs relevant to different organ systems.

The Research Outcomes Assessors (ROAs) conducted a telephone interview with study participants within 72 hours of the baseline visit to complete the baseline $HRSD_{17}$ and the $IDS\text{-}C_{30}$[25,26]. Other research outcomes were collected by IVR within 72 hours of the initial visit, including quality of life as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [33].

Statistical Analyses

Participants were grouped according to baseline score on item #6 of the $IDS\text{-}C_{30}$, which captured irritability at the baseline visit. Groups included the ‘high’ (irritability 50% of the time or greater; item #6 >1) and the ‘low’ (item #6 ≤1) irritability groups. A baseline Hamilton Rating Scale for Depression (HAM-D) Anxiety/ Somatization factor score of ≥7 was considered indicative of anxious depression, as in prior reports[20], and atypical depression was similarly defined according to IDS-C30 items[34]. Descriptive statistics were used to characterize the population. Bivariate logistic regression models were used to assess associations between the independent variable of interest (e.g., race, sex, episode

duration) and the presence of irritability. Logistic regression models were also used to assess the association of the independent variables of interest and the presence of irritability independent of the effect of total depression severity, as measured by the IDS-C_{30} (not including the item used to determine irritability). Statistical significance was defined as a two-sided p-value of less than 0.05.

RESULTS

A total of 4,041 participants were enrolled in STAR*D; 1,500 were considered in the initial report[3] and 2,541 in this report. Of these 2,541 participants, 2,307 had the necessary data available to assess irritability. Of the 2,307 participants in this cohort, 63% were female; 76% were Caucasian, 17% were African-American, and 7% were of other ethnicity; 56% were employed, 38% were unemployed, and 6% were retired; 41% were married, 25% were divorced, 31% never married, and the remaining 3% widowed. Mean age at study entry was 40.5±13.35. Mean age at first episode was 25.7±14.63, and mean duration of current episode was 24.0±50.15 months.

This cohort was generally similar to those reported earlier [3,35], except that the current cohort had more participants recruited from primary care settings (44% vs. 35%, $p<0.001$) and fewer with private insurance (49% vs. 57%, $p<0.001$).

Of the 2,307 individuals who completed the IDS-C_{30}, 1,067 (46%) reported the presence of significant irritability on at least 50% of days in the prior week. Comparisons of subjects with or without significant irritability are displayed in Table 1. Irritability was more common among women, individuals with younger age at study entry, those with fewer years of education, those who were unemployed, and those who were married. Irritability was also associated with significantly greater depression severity at study entry.

To determine whether irritability could be distinguished from anxious depression, we examined the association between individual anxiety symptoms and irritability. The presence of symptoms of anxious mood (crude OR: 2.35), psychomotor agitation (crude OR: 1.87), sympathetic arousal (crude OR: 1.55), and panic/phobic symptoms (crude OR: 2.07) were all significantly associated ($p<.0001$) with irritability. After adjusting for differences in sex, age, and baseline depression severity, none of these odds ratios differed significantly from 1. Irritability in the absence of anxiety symptoms was uncommon: among 1067 subjects reporting irritability, 112 (10.5%) denied having anxious mood, 314 (29.4%) denied having psychomotor agitation, 278 (26.1%) denied experiencing sympathetic arousal, and 184 (17.2%) denied any somatic complaints. Only 11/1067 (1%) denied having all three of these symptoms.

Irritability was also significantly more common among certain anxiety disorder comorbid conditions (Table 1), including generalized anxiety, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, and social phobia. After adjusting for differences in age, sex, and depression severity, significant differences persisted for generalized anxiety and obsessive-compulsive disorder. Significantly more anxious depressed participants met criteria for irritable depression than did non-anxious depressed participants.

We next examined previously suggested clinical correlates of irritability. Current suicidality was associated with irritability (Table 1), though this was attributable to underlying differences in age, sex, and severity. Likewise, among those with a history of lifetime suicide attempts, irritability was more common, and again this difference did not persist after adjustment for age, sex, and severity. Poorer quality of life, as measured by lower score on the Q-LES-Q, was also associated with increased likelihood of irritability.

Finally, we examined those clinical features suggested to be associated with bipolar disorder or bipolar spectrum illness, including family history of bipolarity, early onset of illness, greater episode recurrence, and atypical depression, as well as lifetime suicide attempts. After adjustment for differences in age, sex, and baseline depression severity, none of these features differed significantly between groups (Table 2). In a post-hoc analysis limited to subjects without any axis I comorbidity (n=862), including 323 subjects (37.5%) with irritability, no significant association with any of these putative bipolar spectrum features features was identified ($p>0.25$ for all comparisons).

DISCUSSION

Our results confirm the substantial prevalence of irritability among outpatients with MDD, as previous work by our group and others had suggested [3,6,36,37]. In this cohort, female sex, younger age at study entry, total depression severity as well as symptoms of anxiety were strongly associated with irritability, which is also consistent with previous work[3], though the overlap is far from complete.

To be clinically meaningful, an illness feature or subtype should influence the clinician's understanding of the illness and its likely course. In the case of irritability, its presence appears to be a marker for a more severe form of depression in several respects. Participants who reported irritability described a significantly poorer quality of life and were more likely to report prior suicide attempts and suicidal ideation at study entry, both attributable to greater overall severity. In two cohorts, each of more than 1,500 subjects drawn from a study specifically designed to be representative of clinical populations, we thus find that irritability indicates greater potential morbidity[3]. Assessment of irritability therefore merits consideration in clinical management of depression: irritable patients might be candidates for more aggressive intervention or closer follow-up. Of course, the predictive validity of irritability in other depressed populations, such as those who require hospitalization or exhibit psychotic symptoms, or those with bipolar disorder, remains to be determined.

On the other hand, the presence of irritability during major depressive episodes does not appear to identify a distinct depressive subtype – that is, it does not uniquely capture features of the disorder in the manner suggested for atypical depression, for example.[38] In particular, presence of irritability is associated with greater prevalence of anxiety disorders, and greater depression severity, which may mediate the observed associations with suicidality.

We were unable to confirm a prior finding of an association between irritability and vascular disease [3]. A substantial literature describes anger or its manifestations as risk factors for cardiovascular disease [39–45]. Our failure to replicate the previous finding of an association may be a reflection of the relatively limited cardiovascular morbidity of our cohort as a whole, or the lack of sensitivity of our measures of vascular disease and irritability.

The notion of bipolar spectrum illness – i.e., that some patients who do not meet full diagnostic criteria for bipolar disorder may nonetheless exhibit characteristics of bipolarity – has received increased attention recently [16,22,37,46]. However, we were unable to confirm a recent report [37] that irritability was associated with other bipolar spectrum features. This may be attributable to the fact that the previous report did not consider other possible confounders (age, sex, severity), or other differences between the two cohorts (e.g., a single large outpatient practice vs. a multicenter study using both primary and specialty

care sites). Our finding underscores the limited value of any single clinical feature in labeling a depressive episode as 'bipolar'.[23]

The reliance upon a single 4-point rating scale item for irritability represents a primary limitation of this analysis. Notably, that item distinguishes frequency, but not severity, of irritability; no assessment of the related symptom of impulsivity was included. The inclusion of broader anger measures in future treatment studies would be extremely helpful in characterizing which particular aspects of anger and irritability confer risk for a poorer outcome. The study also lacked a standardized assessment of personality disorders, some of which may be associated with mood lability, anger outbursts, and poorer outcomes. On the other hand, personality disorder diagnoses may not remain stable from acute depressive episodes to remission [47]. Finally, while participants were excluded if they met DSM-IV criteria for bipolar disorder using a clinical evaluation and symptom checklist, the sensitivity of these measures for bipolar II disorder may be limited [48].

Despite these limitations, our results highlight the relatively high prevalence of irritability among outpatients with MDD. While irritable MDD *per se* may not be a distinct subtype, it is also not simply a proxy for more severe or more anxious depression. At the same time, our results confirm the clinical implications of irritability during depressive episodes, again demonstrating an association with poorer quality of life and suicidality. These findings suggest that future studies should place a greater emphasis on the assessment and treatment of irritability as a feature of major depressive episodes.

Significant outcomes

- Irritability is associated with greater depression severity and anxiety
- poorer quality of life
- greater likelihood of prior suicide attempts, and current suicidality.

Limitations

- Findings are based on a single-item ordinal measure of frequency of irritability.

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Declaration of Interests

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Speaker’s Bureau: Cyberonics, Inc.; Forest Pharmaceuticals, Inc.; GlaxoSmithKline.

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Table 1

Clinical features of individuals with major depressive episodes with or without irritability at study entry.

	All patients (N=2307)	%	Irritable depression (N=1067)	%	Nonirritable depression (N=1240)	%	Unadjusted OR	p	Adjusted OR*	p
Socio-demographic features										
Age at baseline (yrs)	40.5±13.3		38.9±12.7		41.8±13.7		0.98	<.0001	**0.98**	<.0001^
Sex: male	865	(37.5)	345	(39.9)	520	(60.1)	0.66	<.0001	**0.79**	0.01^
Education (yrs)	13.4±3.2		13.0±3.1		13.7±3.3		0.93	<.0001	**0.97**	0.01
Employment status								0.01		0.55
Employed	1298	(56.4)	585	(45.1)	713	(54.9)	-		-	
Unemployed	882	(38.3)	437	(49.5)	445	(50.5)	1.20		0.93	
Retired	123	(5.3)	44	(35.8)	79	(64.2)	0.68		1.15	
Marital status								0.02		0.006
Married/cohabiting	951	(41.3)	468	(49.2)	483	(50.8)	-		-	
Never married	709	(30.8)	316	(44.6)	393	(55.4)	0.83		**0.70**	
Divorced/separated	570	(24.8)	258	(45.3)	312	(54.7)	0.85		**0.78**	
Widowed	73	(3.2)	24	(32.9)	49	(67.1)	0.51		**0.62**	
Features of current episode										
Duration (months)	24.0±49.3		26.1±55.2		22.3±43.6		1.04	0.22	**1.08**	0.05
HRSD-17	19.7±6.5		22.1±6.0		17.6±6.1		1.13	<.0001	**1.06**	0.0002
IDS-C30 (less irritability)	34.0±11.1		38.4±10.2		30.2±10.4		1.08	<.0001	**1.08**	<.0001^
QLESQ	41.6±15.4		37.7±15.0		45.0±14.9		0.97	<.0001	0.99	0.08
Suicidal ideation present	1097	(47.6)	581	(53.0)	516	(47.0)	1.68	<.0001	0.95	0.59
Anxious depression	1049	(45.5)	644	(61.4)	405	(38.6)	3.15	<.0001	**1.57**	<.0001
Concurrent axis I disorders or vascular disease										
Agoraphobia	264	(11.6)	164	(62.1)	100	(37.9)	2.09	<.0001	1.17	0.30
Alcohol abuse	267	(11.8)	127	(47.6)	140	(52.4)	1.07	0.61	1.09	0.54
Bulimia	286	(12.6)	154	(53.8)	132	(46.2)	1.43	0.01	1.05	0.75

	All patients (N=2307)	%	Irritable depression (N=1067)	%	Nonirritable depression (N=1240)	%	Unadjusted OR	p	Adjusted OR*	p
Drug abuse	174	(7.7)	88	(50.6)	86	(49.4)	1.21	0.22	1.07	0.70
Generalized anxiety	472	(20.8)	303	(64.2)	169	(35.8)	2.54	<.0001	**1.49**	0.0007
Hypochondriasis	96	(4.2)	56	(58.3)	40	(41.7)	1.67	0.02	1.07	0.76
Obsessive-Compulsive Disorder	316	(13.9)	211	(66.8)	105	(33.2)	2.69	<.0001	**1.91**	<.0001
Panic Disorder	276	(12.2)	169	(61.2)	107	(38.8)	2.01	<.0001	1.03	0.82
PTSD	397	(17.5)	232	(58.4)	165	(41.6)	1.83	<.0001	1.10	0.46
Social phobia	666	(29.4)	372	(55.9)	294	(44.1)	1.74	<.0001	1.15	0.17
Somatoform disorder	49	(2.2)	33	(67.3)	16	(32.7)	2.45	0.00	1.40	0.31
Vascular disease (CIRS)	561	(24.3)	259	(46.2)	302	(53.8)	1.00	0.96	1.16	0.21

Table 2

Putative bipolar spectrum features among individuals with or without irritability at study entry

	All patients (N=2307)	%	Irritable depression (N=1067)	%	Nonirritable depression (N=1240)	%	Unadjusted OR	p	Adjusted OR*	p
Family history, substance abuse	1054	(46.1)	498	(47.2)	556	(52.8)	1.09	0.29	0.99	0.95
Family history, mood disorder								0.91		0.58
None	981	(43.0)	447	(45.6)	534	(54.4)				
Unipolar	1103	(48.4)	511	(46.3)	592	(53.7)	1.03		0.96	
Bipolar	196	(8.6)	92	(46.9)	104	(53.1)	1.06		0.84	
Age at first episode>=18	1415	(62.0)	636	(44.9)	779	(55.1)				
Age at first episode<18	867	(38.0)	421	(48.6)	446	(51.4)	1.16	0.09	0.98	0.80
Recurrence (number of episodes)								0.14		0.14
1	568	(27.0)	260	(45.8)	308	(54.2)				
2	374	(17.8)	179	(47.9)	195	(52.1)	1.09		0.99	
3	309	(14.7)	126	(40.8)	183	(59.2)	0.82		0.72	
4–9	397	(18.9)	176	(44.3)	221	(55.7)	0.94		0.84	
10+	452	(21.5)	225	(49.8)	227	(50.2)	1.17		1.04	
Atypical features	377	(16.3)	212	(56.2)	165	(43.8)	1.62	<.0001	0.88	0.33
Suicide attempt, lifetime	373	(16.2)	194	(52.0)	179	(48.0)	1.32	0.01	0.86	0.23

*after adjustment for baseline differences in age, sex, and depression severity

^after adjustment for baseline differences in the other two potential confounders from among age, sex, depression severity

Abbreviations: HRSD-17, Hamilton Rating Scale for Depression (17 item); IDS-C30, Inventory of Depressive Symptomatology, Clinician Rated (30-item); QLESQ, Quality of Life and Satisfaction Questionnaire. CIRS, Cumulative Illness Rating Scale. See text for details.