Prevalence and Clinical Correlates of Irritability in Major Depressive Disorder: A Preliminary Report From the Sequenced Treatment Alternatives to Relieve Depression Study

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Background: Irritability is a common feature of major depressive disorder (MDD), though it is not included in the DSM-IV diagnostic criteria for adult MDD and is not assessed in most standard depression rating scales. Irritability with or without depression has been associated with risk for suicide, violence, and cardiovascular disease.

Method: The prevalence of significant levels of irritability was examined among the first 1456 outpatients with nonpsychotic MDD entering the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Sociodemographic and clinical features were compared for participants who did and did not report irritability at least 50% of the time during the week preceding study entry.

Results: Of 1456 evaluable subjects, 582 (40%) reported irritability more than half the time. These individuals were more likely than nonirritable subjects to be female, to be younger, to be unemployed, and to report a history of at least 1 suicide attempt. Functional status and quality of life were also poorer in this group. Irritability was correlated with overall depressive severity, which accounted for nearly all of the clinical differences noted, with the exception of vascular disease, for which the association persisted after controlling for age, sex, and depressive severity.

Conclusion: Irritability is prevalent among depressed outpatients and associated with a greater likelihood of suicide attempts, poorer functional status, and greater prevalence of vascular disease. It is correlated with overall depression severity and thus may not represent a distinct depressive subtype per se. The impact of irritability on course and treatment outcome merits further study.

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Under DSM-IV criteria, irritability is considered a diagnostic feature of major depressive disorder (MDD) only in children and adolescents.[1] Most standard rating scales of depressive symptom severity do not specifically measure irritability.[2,3] Indeed, irritability itself is a concept not applied consistently in psychiatric research, in which irritability—proneness to anger—is rarely distinguished from hostility, aggression, or anger itself.[4]

Irritability appears to be a common feature of depressive episodes.[5–9] Since the initial description of a hostile, mistrustful depressive subtype in 1966,[10] subsequent studies have reported a prevalence of irritability between 34% and 60%.[7–9] A particular form of irritable depression marked by recurrent anger attacks, spontaneous episodes characterized by feelings of rage and symptoms of physiologic arousal similar to panic attacks and accompanied by chronic irritability, was identified in 20% to 60% of patients with unipolar depression[11,12] and nearly two thirds of patients with bipolar depression.[100]

Several studies have suggested that the presence of irritability may be associated with greater morbidity in

patients with depressive and bipolar disorder. Anger, irritability, and hostility have been associated with treatment nonadherence,[13,14] suicide attempts,[13,15–20] violence,[21] and accidents.[19] Likewise, anger in various forms has been associated with cardiovascular morbidity or mortality.[22–31] While depression itself has also been shown to increase cardiovascular risk,[32–39] the possible additive effect of irritability in the context of MDD is not well studied.

Unfortunately, nearly all of these studies rely on different measures or definitions of hostility, irritability, or anger, limiting comparisons and the feasibility of assessment in clinical practice. Therefore, to better understand the prevalence and possible clinical relevance of irritability in MDD, we examined a simple clinical rating of irritable depression, and its sociodemographic and clinical correlates, in a large cohort of patients with MDD at entry into a multicenter effectiveness trial, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[40,41] We examined in particular the relationship of irritability with depressive severity and symptomatology, sociodemographic features, concurrent illness, and other features of illness course, as well as with quality of life and functioning.

METHOD

The methods of the STAR*D study are described in detail elsewhere.[40,41,53] In brief, STAR*D is a prospective investigation of treatments for outpatients with nonpsychotic MDD who have had an unsatisfactory clinical response to initial treatment with a selective serotonin reuptake inhibitor (SSRI). Subjects in this report were evaluated at baseline, before SSRI resistance was documented in a prospective open trial.

Study Organization

The STAR*D study includes 14 regional centers across the United States, each of which conducts the protocol at between 2 and 4 clinical sites. Of the 41 sites, 19 are primary care settings and the remainder are specialty care settings.

Study Population

Recruitment. STAR*D will recruit 4000 participants for initial treatment with the SSRI citalopram. This preliminary report presents data from the initial 1500 subjects. Since advertising may attract a less representative population of participants, advertisements are not used for recruitment.[38] All risks, benefits, and adverse events associated with each treatment in the study are explained to study participants, who must provide written informed consent prior to study entry.

Inclusion/exclusion criteria. Participants are male or female outpatients, aged 18 to 75 years, with nonpsychotic MDD and a baseline 17-item Hamilton Rating Scale for Depression (HAM-D-17) score of ≥ 14, for whom treating clinicians have determined that outpatient antidepressant treatment is safe and appropriate. Exclusionary diagnoses include schizophrenia, schizoaffective disorder, bipolar disorder, anorexia nervosa, bulimia nervosa, and obsessive-compulsive disorder. Individuals with current substance abuse or dependence are study eligible, provided that inpatient detoxification is not required clinically; these individuals are also encouraged to participate in a substance abuse program. Individuals are also excluded if they have a well-documented history of nonresponse to, or clear intolerance of, adequate doses of an SSRI or one of the other medications utilized in second-step treatment in the protocol during the current major depressive episode. Participants are also excluded if they are already receiving a specific psychotherapy for depression. Other exclusions include severe, unstable concurrent psychiatric conditions that are likely to require hospitalization within 6 months (e.g., severe alcohol dependence with recent detoxification admissions) and concurrent medical or psychiatric conditions that are contraindications to the use of more than 1 treatment option within the protocol, so that randomization to any of the next-step treatment strategies would be impossible.[40,41] Concomitant use of non-psychotropic medications, or anxiolytics and sedative-hypnotics, is not exclusionary provided the patient's clinician determines that protocol-specified antidepressants will still represent safe and appropriate treatments. Finally, participants who are pregnant or who are trying to become pregnant are also excluded.

Data Collection

After written informed consent is obtained at the screening/baseline visit, information collected by semistructured interview includes clinical and demographic data, prior course of illness, current and past substance abuse, prior suicide attempts, family history of mood disorders, current general medical illnesses, and prior history of treatment (both medication and psychotherapy) in the current major depressive episode. Participants complete a modified version of the Psychiatric Diagnostic Screening Questionnaire (PDSQ)[42] assessing types and degree of concurrent psychiatric symptoms. This measure yields a score for each of 11 DSM-IV Axis I diagnoses, reflecting the number of symptom items on the PDSQ endorsed by the patient that were relevant to each diagnosis.

The clinical research coordinator at the study site completes the HAM-D-17 at baseline, as well as the 16-item Quick Inventory of Depressive Symptomatology (QIDS-C16),[43,44] and reviews inclusion/exclusion criteria. The QIDS-C16 is a clinician-rated scale assessing 9 diagnostic symptoms/domains of MDD. Current general medical conditions are assessed with the 14-item Cumulative Illness Rating Scale (CIRS),[45,46] completed using a scor-

ing manual that scores the severity/morbidity of general medical conditions for each of 14 organ systems from 0 to 4. A score of 0 represents "no problem," 1 is "current mild or past significant problem," 2 is "moderate disability requiring first-line treatment," 3 is "uncontrollable chronic problems or significant disability," and 4 is "end organ failure requiring immediate treatment." A total CIRS score is calculated by summing the severity score for the organ systems. The CIRS includes as vascular diseases hypertension, peripheral atherosclerotic disease, intracranial vascular event, and aortic aneurysm.

Patient data are also 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). The ROA conducts a telephone interview within 72 hours of this baseline visit to complete the baseline HAM-D-17 and the 30-item Inventory of Depressive Symptomatology–Clinician-Rated (IDS-C30) using a semistructured interview.[44,47] Item 6 of the IDS-C30 assesses irritability on a 0-to-3 scale, with 3 probe questions: "Have you felt irritable in the past week?" "Have you found yourself becoming more easily angered or irritated by others?" and "How much of the time in this past week?" On this item, 0 represents "does not feel irritable," 1 represents "feels irritable less than half the time," 2 represents "feels irritable more than half the time," and 3 represents "feels extremely irritable virtually all the time."

Other research outcomes are collected by the IVR system[48] within 72 hours of the initial visit; these include measures of function (the Work and Social Adjustment Scale [WSAS][49] and the 12-Item Short-Form Health Survey [SF-12][50]) and quality of life (the Quality of Life and Enjoyment Satisfaction Questionnaire [Q-LES-Q][51]).

Statistical Analysis

The distribution of irritability scores on item 6 of the IDS-C30 collected by the ROA at the baseline visit was examined first. To facilitate comparisons, patients were grouped according to this item, which captures irritability at baseline visit, into "high" (irritability greater than 50% of the time; item 6 score ≥ 2) versus "low" (item 6 score ≤ 1) irritability groups. The a priori decision to dichotomize this value for all analyses was intended to simplify exploratory analyses and was based on the correspondence of the item with an easily assessed clinical measure ("more or less than half the time").

Overall depression severity was examined using simple correlation, and the relationship between presence or absence of high irritability and presence or absence of other depressive symptoms, adjusted for age, sex, and depression severity, was examined using logistic regression models. The relationship between irritability and sociodemographic features such as age and marital status, features of disease course such as recurrence and episode length, and concurrent psychiatric and medical illness was also examined using logistic regression with adjustment for potential confounding by age, sex, and total depression severity, as measured by the IDS-C30 total score (collected by the ROA) excluding item 6. Finally, linear regression models were used to examine the association between irritability and measures of function and quality of life.

Consistent with prior reports, anxious depression was defined as MDD with high levels of anxiety symptoms (HAM-D-17 anxiety/somatization factor score ≥ 7).[52,53] The anxiety/somatization factor, derived from a factor analysis of the HAM-D-17,[54] includes 6 items from the original 17-item version: 10, anxiety (psychic); 11, anxiety (somatic); 12, somatic symptoms (gastrointestinal); 13, somatic symptoms (general); 15, hypochondriasis; and 17, insight. The HAM-D-17 score used to define anxious depression was the one obtained at baseline by the ROAs.

Statistical significance was defined as a 2-sided p value of less than .05. Because these analyses are intended to be exploratory and hypothesis-generating, no adjustments to p values were made for multiple comparisons, so caution is advised in interpreting positive results until replicated.

RESULTS

As has been reported elsewhere,[53] among the initial 1500 STAR*D participants, 63% were female, with a mean age of 40.4 years at study entry. Baseline depression severity as measured with the HAM-D-17 was 20.4 (SD = 6.6), in the moderate to marked range. Baseline ROA assessments including IDS-C30 were available for 1456 of these individuals.

In this sample, on baseline IDS-C30, 9.6% of patients described irritability nearly all the time; 30.4% described irritability more than half the time; an additional 40.8% described some irritability, but less than half the time; and 19.2% denied irritability. Therefore, 40.0% of the sample was classified as having high irritability and the remainder as having low irritability. Irritability was correlated with depression severity as assessed by total IDS-C30 score, not including the irritability item ($r = 0.35$, $p < .0001$). A similar relationship was observed for HAM-D-17 and IDS self-report measures of severity.

We next examined the presence or absence of individual items on the IDS to determine their relationship and degree of overlap with irritability. While nearly all items were associated with irritability in unadjusted analyses (results not shown), only 3—all neurovegetative symptoms—persisted after adjustment for severity. Midnocturnal insomnia (OR = 1.45, 95% CI = 1.04 to 2.02) was associated with higher rates of irritable depression, while weight loss (OR = 0.60, 95% CI = 0.47 to 0.77) and low energy (OR = 0.55, 95% CI = 0.36 to 0.85) each were associated with lower rates of irritable depression.

Table 1. Sociodemographic Features of Major Depressive Disorder (MDD) Patients With and Without Irritability

Characteristic	N[a]	High Irritability[b]	Low Irritability	OR (95% CI)	OR (95% CI), Adjusted[c]
Age at entry, mean (SD), y	1454	38.6 (12.3)	41.8 (13.6)	0.98 (0.97 to 0.99)	0.98 (0.97 to 0.99)
Education, mean (SD), y	1452	13.0 (3.2)	13.9 (3.2)	0.91 (0.88 to 0.95)	0.94 (0.91 to 0.97)
Monthly income, mean (SD), $	1456	2106 (2593)	2622 (3141)	0.97 (0.93 to 1.02)	1.00 (0.95 to 1.04)
Gender, N (%)					
Male	540	185 (34)	355 (66)	0.68 (0.55 to 0.85)	0.75 (0.59 to 0.94)
Female	910	394 (43)	516 (57)		
Marital status, N (%)					
Never married	410	162 (40)	248 (60)	0.98 (0.76 to 1.26)	0.71 (0.53 to 0.95)
Married	618	249 (40)	369 (60)		
Divorced	388	158 (41)	230 (59)	1.02 (0.79 to 1.32)	0.95 (0.72 to 1.26)
Employment status, N (%)					
Unemployed	505	224 (44)	281 (56)	1.27 (1.02 to 1.59)	1.10 (0.64 to 1.40)
Employed	857	330 (39)	527 (61)		
Family history of MDD, N (%)					
Yes	810	321 (40)	489 (60)	0.96 (0.78 to 1.19)	0.89 (0.71 to 1.12)
No	641	260 (41)	381 (59)		

[a]N = 1456 for total sample; N < 1456 reflects missing sociodemographic data for some subjects.
[b]Defined as IDS-C30 item 6 score ≥ 2, i.e., irritability present greater than 50% of the time during the preceding week.
[c]Adjusted for age at study entry, gender, and depression severity (IDS-C30 total score, without irritability item).
Abbreviation: IDS-C30 = 30-item Inventory of Depressive Symptomatology–Clinician-Rated.

Sociodemographic features of those with high irritability (more than half the time) (N = 582) and low irritability (less than half the time or never) (N = 874) are depicted in Table 1. Irritability was more common among women, younger individuals, those with less education, and those who were currently unemployed.

Other features of disease course are displayed in Table 2. Age at onset was earlier among subjects with irritability, although this difference was accounted for by adjusting for baseline severity, age, and sex; number of depressive episodes and duration of index episode were similar in the 2 groups. Subjects with anxious depression were also more likely to meet criteria for irritable depression,[53] although this association did not persist after correction for confounding variables. Irritable depressed patients were also more likely to have made at least 1 suicide attempt. This association also did not persist after controlling for the confounding variables.

We examined the prevalence of concurrent psychiatric and general medical illness among irritable and nonirritable subjects (Table 2). There was no association between the number of alcohol or substance use symptoms endorsed on the PDSQ and the presence of irritable depression. The odds of the presence of irritable depression were 5.9% higher for each additional symptom of generalized anxiety endorsed on the PDSQ after controlling for severity of depression, sex, and age. Notably, while there was no association with overall burden of general medical illness, irritable depression was more prevalent among those with vascular disease, with an adjusted odds ratio of 1.43 (95% CI = 1.06 to 1.93).

Finally, the impact of irritability on functioning and quality of life was examined in linear regression models, with irritable depression as the primary predictor. Q-LES-Q, WSAS, and SF-12 (mental health) scores all indicated greater impairment among subjects with irritable depression ($p < .0001$ for all comparisons). These differences were no longer statistically significant after the effect of depression severity was included in the models.

DISCUSSION

Our results indicate that substantial levels of irritability are commonly found among adult outpatients with MDD, present greater than 50% of the time for 40% of the participants in this study. The particular measure does not correspond to any used in previous studies, and the patient samples differ between studies, so direct comparisons with those studies are impossible, but this prevalence appears generally similar to that previously described.[55,56] For example, one of the earliest descriptions of hostile depression found a prevalence of 34%,[7] while a study of depressed inpatients reported a prevalence of 36%.[9]

Irritability is often considered together with anxiety; in a factor analysis, it appeared to be best captured by a common anxiety/irritability factor.[57] One model posits that these symptoms represent markers of a trait sometimes referred to as negative affectivity—that is, sensitivity to negative stimuli.[58] Anxiety appears to carry clinical significance in MDD.[53] Our results suggest that the overlap between anxiety and irritability is incomplete, whether measured as concurrent symptoms suggesting generalized anxiety or individual items on a depression rating scale.

The degree of irritability appears to be highly correlated with overall depression severity, accounting for many of the clinical differences we observed in this cohort. This finding is consistent with some previous studies, despite differences in methodology.[59–61] Therefore,

Table 2. Lifetime Illness Course and Features of Current Episode in Major Depressive Disorder (MDD) Patients With High and Low Irritability

Variable	N[a]	High Irritability[b]	Low Irritability	OR (95% CI)	OR (95% CI), Adjusted[c]
Age at onset of first MDE, mean (SD), y	1444	23.8 (12.8)	26.1 (14.6)	0.98 (0.97 to 0.99)	1.00 (0.99 to 1.01)
No. of prior episodes, mean (SD)	1329	6.4 (10.3)	5.3 (8.7)	1.10 (0.96 to 1.26)	1.14 (0.98 to 1.32)
Duration of current episode, mean (SD), mo	1334	21.8 (51.6)	21.0 (53.1)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
HAM-D-17 score, mean (SD)	1456	22.6 (6.0)	19.0 (6.6)	1.10 (1.08 to 1.12)	1.00 (0.97 to 1.04)
Concurrent symptoms, mean (SD)[d]					
Alcohol use disorder (PDSQ)	1447	0.6 (1.4)	0.7 (1.5)	0.94 (0.87 to 1.01)	0.92 (0.85 to 1.00)
Substance use disorder (PDSQ)	1445	0.3 (1.1)	0.3 (1.1)	0.98 (0.89 to 1.07)	0.92 (0.83 to 1.02)
Generalized anxiety (PDSQ)	1440	7.3 (2.8)	6.2 (3.2)	1.14 (1.10 to 1.18)	1.06 (1.02 to 1.10)
CIRS score (total)	1437	4.4 (3.7)	4.2 (3.6)	1.01 (0.98 to 1.04)	1.03 (0.99 to 1.06)
Anxious subtype, N (%)[e]					
Yes	1066	479 (45)	587 (55)	2.29 (1.77 to 2.96)	0.95 (0.69 to 1.30)
No	384	101 (26)	283 (74)		
Attempted suicide (ever), N (%)					
Yes	256	124 (48)	132 (52)	1.52 (1.16 to 2.00)	1.12 (0.83 to 1.51)
No	1195	457 (38)	738 (62)		
Concurrent or comorbid illness, N (%)[f]					
Cardiac disease					
Yes	222	89 (40)	133 (60)	0.99 (0.74 to 1.32)	1.11 (0.80 to 1.53)
No	1229	489 (40)	740 (60)		
Vascular disease					
Yes	311	129 (42)	182 (59)	1.07 (0.83 to 1.38)	1.43 (1.06 to 1.93)
No	1140	448 (39)	692 (61)		

[a]N = 1456 for total sample; N < 1456 reflects missing sociodemographic data for some subjects.
[b]Defined as IDS-C30 item 6 score ≥ 2, i.e., irritability present greater than 50% of the time during the preceding week.
[c]Adjusted for age at entry, gender, and depression severity (IDS-C30 total score, without irritability item).
[d]PDSQ scores refer to number of DSM-IV diagnostic criteria reported by the patient as present, and CIRS scores refer to total severity score.
[e]Anxious depression defined as MDD with HAM-D-17 anxiety/somatization factor score ≥ 7; see Method for details.
[f]For each organ system, "yes" refers to CIRS organ system score > 0.
Abbreviations: CIRS = Cumulative Illness Rating Scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, IDS-C30 = 30-item Inventory of Depressive Symptomatology–Clinician-Rated, MDE = major depressive episode, PDSQ = Psychiatric Diagnostic Screening Questionnaire.

irritability may be best understood as a broad indicator of more severe depression and in this sense may be useful in the clinical evaluation of the depressed patient. Furthermore, because it does correlate well with overall severity, it would be worthwhile to consider evaluating irritability in future clinical trials and to examine its diagnostic value.

The presence of irritability appeared to have significant associations with clinical course, including greater prior history of suicide attempt and poorer current functioning. The association between irritability and suicide attempts is consistent with previous reports.[15–20] Most of these prior reports failed to control for depression severity; it may be overall severity, rather than irritability, that is associated with suicide risk. However, relative to overall depression severity, irritability is more easily and rapidly assessed, so it may be useful to examine irritability as part of a standard evaluation for suicide risk.

To our knowledge, this study is also one of the first to investigate the possible clinical correlates of irritability in a sizeable sample of outpatients with nonpsychotic MDD. Prospectively, depression has previously been associated with an increased risk of hypertension,[62–64] coronary heart disease incidence,[35,65–70] heart failure,[34,37] and cardiac events[38,71,72] including myocardial infarction.[73,74] Likewise, anger, irritability, and hostility have been associated with cardiovascular morbidity or mortality,* including hypertension[80,82,83] and hemodynamic reactivity.[84] Consistent with these reports, we found an association between the presence of significant irritability and vascular disease, evident only after controlling for differences in sex, age, and overall depression severity, all of which are reported to influence vascular disease.[26,29,85–89] The absence of association with cardiac disease may reflect the relatively young study population.

While we note an association between irritability and vascular disease, we cannot infer causation, a limitation that applies to any cross-sectional analysis. However, an important question for future investigation will be the extent to which irritability and related symptoms either mediate cardiovascular risk in depression or confer additional risk. It is notable that anger attacks in depression have been associated with higher cholesterol levels[90] and other risk factors for cardiovascular disease.

A constraint of this study is its reliance on a single measure of irritability, which is likely to be less reliable than a rating scale composed of multiple items. To allow more clinically interpretable reporting of results, we utilized this item as a dichotomous measure (irritability more or less than 50% of the time) rather than an ordinal

*References 22–24, 26, 28, 63, 66, 75–81.

one. That measure also captures only one aspect of irritability—frequency—while failing to examine severity or potential consequences (physical violence, for example) and clinical correlates (anger outbursts, for example). Therefore, it probably overlaps only partially with other irritable subtypes previously described, such as depression with anger attacks, as the latter includes irritability as a core symptom but requires frequent outbursts of anger as well.[5] Conversely, the variability introduced by reliance on a single measure is balanced by a large, systematically assessed sample. In future studies, the inclusion of broader examinations of irritability such as the State-Trait Anger Expression Inventory 2[91]; Anger, Irritability, and Assault Questionnaire[92]; and Anger Attacks Questionnaire[93] would be helpful in clarifying the aspects of irritability that are most relevant.

An additional limitation is the use of multiple comparisons, without adjustment of alpha, raising the risk of type I error. However, we adopted this approach as this analysis was designed a priori to use data from the first group of patients to enter STAR*D to generate hypotheses for future study of irritable depression. We intend to confirm these results in the second cohort of patients from the STAR*D study.

A third limitation is our inability to clarify the relationship between irritable depression and comorbid personality disorders or other diagnoses. The complexity of the relationship between temperament, personality, and mood is well established.[94] For example, the nature of depressive symptoms may be influenced by personality traits; in this model, irritability may be one manifestation of sensitivity to negative stimuli[58] or interpersonal sensitivity.[95] STAR*D does not include systematic assessment of personality disorders. However, the assessment of personality disorders during a depressive episode is difficult in any case: apparent disorders may change markedly during the course of treatment.[96]

In addition to the potential overlap with personality disorders, irritability and behavioral dyscontrol have been suggested as precursors to or markers of bipolar disorder in children[97–99] and adults.[100–102] However, all subjects in the present study were evaluated for bipolar disorder clinically and with a symptom checklist and were excluded if they met DSM-IV criteria for bipolar disorder, so it is unlikely that the irritable depressed subjects were actually misdiagnosed bipolar patients experiencing mixed or manic episodes.

In sum, irritable depression, defined as MDD with frequent irritable mood, may not represent a distinct depressive subtype per se, but rather a variant of MDD associated with greater depression severity as well as with vascular morbidity.

Functional neuroimaging[103,104] and genetic[105,106] investigations suggest different biological substrates or risk factors for irritability than for depression as a whole. Because irritability is prevalent, and appears to be associated with poorer functioning, greater likelihood of prior suicide attempts, and greater vascular morbidity, it merits more attention in future clinical and neurobiological investigations in MDD. In addition, the possibility that psychopharmacologic or cognitive-behavioral interventions specifically targeting irritability provide an opportunity to influence these outcomes merits further study.

Drug name: citalopram (Celexa).

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