Overt Irritability/Anger in Unipolar Major Depressive Episodes Past and Current Characteristics and Implications for Long-term Course

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**IMPORTANCE** Although symptoms of irritability or anger are not central to the diagnosis of unipolar major depressive episodes (MDEs), these symptoms have been found, in cross-sectional studies, to be highly prevalent and associated with increased comorbidity and depressive illness burden.

**OBJECTIVE** To determine the prevalence of overtly expressed irritability/anger and its effect on intake presentation and the long-term course of illness.

**DESIGN** A prospective, naturalistic investigation of patients with unipolar MDEs, studied systematically at intake and during up to 31 years of follow-up.

**SETTING** Five US academic medical centers.

**PARTICIPANTS** Patients entered the National Institute of Mental Health Collaborative Depression Study during an MDE in 1978, 1979, 1980, or 1981. Patients with unipolar MDE at intake (n = 536) were divided into those with and those without current comorbid overtly expressed irritability/anger.

**EXPOSURE** In this observational, longitudinal study, patients received treatment that was recorded but not controlled.

**MAIN OUTCOMES AND MEASURES** Groups were compared on illness severity and chronicity, psychosocial impairment, quality of life, suicidal behavior, lifetime comorbid diagnoses, impulse control, and measures associated with bipolarity.

**RESULTS** Overt irritability/anger was present in 292 of 536 participants with a unipolar MDE at study intake (54.5%). It was associated with significantly increased depressive severity, longer duration of the index MDE, poorer impulse control, a more chronic and severe long-term course of illness, higher rates of lifetime comorbid substance abuse and anxiety disorder, more antisocial personality disorders, greater psychosocial impairment before intake and during follow-up, reduced life satisfaction, and a higher rate of bipolar II disorder in relatives. No association was found with increased suicidal ideation or behavior. Results were not explained by comorbidity or other manic spectrum symptoms.

**CONCLUSIONS AND RELEVANCE** This study extends results of cross-sectional investigations and indicates that irritability/anger during MDEs is a highly prevalent clinical marker of a more severe, chronic, and complex depressive illness. Findings have important implications for assessment and treatment.

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Irritability/anger has long been recognized as a symptom commonly seen during major depressive episodes (MDEs). This symptom was integral to the diagnosis of MDE until 1987, when it was dropped as a diagnostic criterion for adults but not for children and adolescents.\(^3\)

Cross-sectional studies have recently reported on the high prevalence of irritability/anger during unipolar MDEs, using different definitions and measures.\(^4\) Benazzi and Akiskal\(^4\) found overtly expressed “irritable-hostile” depression in 37% of 254 patients who experienced a unipolar MDE. It was associated with younger age, younger age at onset of mood disorders, atypical depressive features, 3 or more concurrent hypomanic symptoms, and a family history of bipolar disorder. In 2307 participants who experienced a unipolar MDE in the Sequenced Treatment Alternatives to Relieve Depression study, Perlis and colleagues\(^5\) defined irritability/anger more broadly, based on subjective feelings of irritability during at least 50% of the time in the previous week using item 6 of the 30-item clinician-rated Inventory of Depressive Symptoms.\(^7\) An irritable mood occurred for 46% of participants with MDEs and was significantly linked to female sex, younger age, greater depressive severity, increased comorbid anxiety disorders, poorer subjective satisfaction and quality of life, a greater history of any prior suicide attempts, higher current suicidal ideation, and a higher rate of atypical depressive features. Using a US household survey of 9224 adults in the National Comorbidity Survey Replication, Fava and colleagues\(^8\) reported that 51% of 955 respondents with a nonbipolar MDE were “irritable, grouchy, or in a bad mood” most every day during the worst 2 weeks of their worst lifetime MDE. Feeling irritable/grouchy was associated with significantly younger age, earlier age at onset of mood disorders, and higher rates of comorbid anxiety and impulse-control disorders, as well as drug (but not alcohol) dependence, longer duration of MDEs, and higher prevalence of symptoms of fatigue and self-reproach during MDEs—but not with greater depressive severity.

The National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS)\(^8,9\) provides a unique opportunity to examine the association of irritability/anger during the intake MDE with important clinical features occurring before study intake, at study intake, and during long-term follow-up (up to 31 years) in a large clinical cohort with systematically diagnosed unipolar MDEs.

### Methods

#### Participants

The participants enrolled in the NIMH CDS\(^8,9\) at 5 academic medical centers (Boston, Massachusetts; Chicago, Illinois; Iowa City, Iowa; New York, New York; and St Louis, Missouri), from 1978 to 1981, while seeking treatment for a major affective episode. Diagnoses at study intake were made using Research Diagnostic Criteria (RDC)\(^10\) based on Schedule for Affective Disorders and Schizophrenia (SADS) interviews,\(^11\) as well as available medical and research records. Patients entering the CDS during a definite MDE with no prior history of bipolar disorder (type I or II) were selected for analysis. After excluding participants who showed any evidence of schizophrenia or schizoaffective disorder by the end of follow-up, a total of 536 participants with a unipolar MDE at study intake made up the analysis sample. Unlike our prior studies of the course of unipolar major depressive disorder (MDD),\(^12-15\) we included 107 participants (20.0% of the sample) who developed their first lifetime mania or hypomania during follow-up, because conversion to bipolar disorder (type I or II) was an outcome of interest.

All patients in the CDS were required to be white (to test genetic hypotheses), speak English, have an IQ score of at least 70, and have no evidence of organic brain syndrome or terminal medical illness. Written informed consent was obtained at each of the 5 sites for participation in the research.

#### SADS Assessment of Overt Irritability/Anger

The SADS items assess overtly expressed irritability, anger, or annoyance during 2 time periods—the worst week of the study intake MDE and the week prior to the SADS interview. Instructions specify that symptoms of irritability in the presence of other manic/hypomanic symptoms were to be excluded. Suggested interview prompts and response options emphasize overt irritability/anger rather than mere feelings. Descriptors for severity ratings, specific to each SADS item, are as follows for overt irritability/anger: 1 = not at all, or only associated with other manic/hypomanic symptoms; 2 = slight (eg, occasional snappiness of doubtful clinical significance); 3 = mild (eg, somewhat argumentative or quick to express annoyance); 4 = moderate (eg, often shouts or loses temper); 5 = severe (eg, throws things, breaks windows, or is occasionally assaultive); and 6 = extreme (eg, repeatedly violent against things or people). In keeping with the SADS rating convention, we considered overt irritability/anger to be “clinically significant” if rated 3 or above on the severity scale, for the worst week, the past week, or both. Over half the sample had clinically significant overt irritability/anger during their study intake MDEs (292 of 536 participants [54.5%]) and are referred to hereafter as the “irritable group.” This group was compared with the “nonirritable group” (244 of 536 participants [44.5%]).

#### Measures on Which the 2 Analysis Groups Were Compared

The CDS contains a remarkable set of data on patient characteristics at study intake and during follow-up. The study intake SADS interview provided information on MDE severity and suicidality (prior to and during study intake). A battery measuring 17 standardized personality characteristics with relevance to affective disorders was administered soon after study intake. The RDC diagnoses were made at study intake and updated at 2 and 5 years, and at subsequent 5-year intervals. For 59.3% of the analysis sample, affective diagnoses were obtained for 1 or more first-degree relatives (biological parents, siblings, or children) from lifetime RDC, based on lifetime SADS interviews. As described in detail elsewhere,\(^11\) trained professional raters interviewed patients every 6 months during the first 5 years of follow-up and yearly thereafter, using variations of the Longitudinal Inter-
val Follow-up Evaluation (LIFE). Weekly Psychiatric Status Ratings in the LIFE forms are linked, as previously described, to diagnostic thresholds and were used to identify the start week and the end week of affective episodes during follow-up, as well as to create summary measures of illness chronicity and severity. Information on suicide attempts was obtained from LIFE interviews and from separate forms reporting suicidal behavior during follow-up. Because the wording and timeframe for ratings of psychosocial impairment changed after the period when the original LIFE form was used, LIFE variants provided monthly ratings of psychosocial impairment analyzed herein for all months of follow-up years 3 to 5 and the final month of years 6 to 31.

The 536 patients entering the CDS during a unipolar MDE, with no lifetime schizophrenia or schizoaffective disorder by the end of follow-up, were systematically followed up for a mean (SD) of 16.2 (10.3) years, with a median of 17.0 years, and no significant difference between the analysis groups. A small portion of the sample (8.4%) participated in follow-up for less than 2 years, while 25.7% were followed for 2 to less than 10 years, 20.5% for 10 to less than 20 years, 40.3% for 20 to less than 30 years, and 5.0% for 30 or 31 years. With 45.3% of the sample followed up systematically for 20 years or more, the CDS provides a unique resource for examining the long-term course of unipolar MDD.

Statistical Analyses
Statistical comparisons between participants with a unipolar MDE with overt clinically significant irritability/anger at study intake and those with a unipolar MDE without overt clinically significant irritability/anger at study intake were made by means of analysis of variance (t tests) for continuous variables if normally or nearly normally distributed, or by means of Wilcoxon rank sum tests if nonnormally distributed. The $\chi^2$ or Fisher exact tests were used for categorical variables, and Wilcoxon $\chi^2$ tests were used on survival function distributions for time to remission/recovery from the study intake MDE and time to subsequent relapse. Study intake personality measures were analyzed by analysis of variance, covarying for age and sex. Finally, we determined whether key outcome variables differed by study intake group after covarying for each of the 3 available RDC categories of current comorbidity (any substance abuse disorder, any anxiety disorder, and any RDC disorder).

A 2-tailed a level of .05 was used to determine statistical significance. Adjustments for multiple comparisons were not made for 2 reasons. First, to the extent that multiple dependent variables are correlated, the Bonferroni adjustment results in an increasing number of type II errors (ie, the failure to detect true differences). Subgroups of dependent variables in the study, such as those related to depressive severity, psychosocial function, or long-term course, are highly intercorrelated. Second, we believe that it is most useful if actual probability values are given for each dependent variable because the consistency of findings across related variables supports the overall findings about that area.

Results

Demographics and Clinical History at Study Intake
The irritable group was significantly younger than the nonirritable group ($P = .002$), had a higher percentage of female participants ($P = .02$), had a lower percentage of participants with at least some college education ($P = .03$), and had an earlier age at onset of their first lifetime affective episodes ($P = .03$) (Table 1).

Characteristics of the Study Intake MDE

Primary/Secondary MDE
Half (49.3%) of the irritable group and 65.2% of the nonirritable group had a primary MDE at study intake (ie, MDE not preceded in time by another Axis I diagnosis) ($P = .001$).

Study Intake MDE Severity and Duration
The Global Assessment Scale measures of overall severity of the study intake MDE were similar for the irritable and nonirritable groups. However, the irritable group had significantly more severe depressive symptoms at study intake ($P = .006$) as measured by the CDS “extracted Hamilton” score (sum of all 17 items of the SADS measuring the severity of MDE diagnostic symptoms). The duration of the study intake MDE, from onset to remission/recovery, was also significantly longer for the irritable group (median duration, 91 weeks) than for the nonirritable group (median duration, 49 weeks) ($P = .002$).

Features of Atypical Depression
We did not find significant differences on any SADS item assessing symptoms of DSM-IV-TR atypical depression (ie, hypersomnia, hyperphagia, mood reactivity, or leaden paralysis).

Poor Impulse Control
In a population study, irritability/anger during unipolar MDEs was associated with low impulse control. The CDS group with overt irritability/anger had significantly lower scores on the Ego Control scale ($P = .009$) of the revised Minnesota Multiphasic Personality Inventory$^{13}$ and the Restraint scale ($P = .01$) of the Guilford-Zimmerman Temperament Survey$^{27}$ (eTable 1 in Supplement). Compared with the nonirritable group, the irritable group also had a significantly higher percentage of participants who engaged in irresponsible, antisocial, or reckless behavior during their study intake MDEs (SADS item 417; 18.2% vs 10.2%; $\chi^2 = 6.68$; $P = .01$) or who had a lifetime diagnosis of antisocial personality disorder at study intake (4.8% vs 1.2%; $P = .02$, determined by use of the Fisher exact test).

Longitudinal Course

Length of First Well Interval
Survival analysis showed a nonsignificant difference between the 2 groups in the length of time from the end of the intake MDE to the start of the subsequent affective episode (Table 2). Although the irritable group had a nonsignificantly shorter median length of time out of any RDC affective episode (144 vs 195 weeks) and a lower probability of remaining...
Table 1. Demographic, Clinical History, and MDE Characteristics for Groups Defined by Clinically Significant Symptoms of Overt Irritability During Study Intake Unipolar MDEs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With Overt Irritability (n = 292)</th>
<th>Without Overt Irritability (n = 244)</th>
<th>Significance Value With df</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>37.5 (12.7)</td>
<td>41.5 (16.4)</td>
<td>$t_{452.8} = 3.15^a$</td>
<td>.002</td>
</tr>
<tr>
<td>Age group, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-34 y</td>
<td>140 (47.9)</td>
<td>114 (46.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-59 y</td>
<td>132 (45.2)</td>
<td>83 (34.0)</td>
<td>$X^2 = 20.6$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥60 y</td>
<td>20 (6.8)</td>
<td>47 (19.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>192 (65.8)</td>
<td>137 (56.2)</td>
<td>$X^2 = 5.17$</td>
<td>.02</td>
</tr>
<tr>
<td>Some college education</td>
<td>142 (49.0)</td>
<td>143 (58.6)</td>
<td>$X^2 = 4.95$</td>
<td>.03</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married or living together</td>
<td>145 (50.0)</td>
<td>116 (47.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Separated, widowed, or divorced</td>
<td>69 (23.8)</td>
<td>53 (21.7)</td>
<td>$X^2 = 1.37$</td>
<td>.50</td>
</tr>
<tr>
<td>Never married</td>
<td>76 (26.2)</td>
<td>75 (30.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of 1st affective episode, mean (SD), y</td>
<td>27.6 (12.2)</td>
<td>30.4 (15.8)</td>
<td>$t_{450.5} = 2.22^a$</td>
<td>.03</td>
</tr>
<tr>
<td>Onset before 21 y</td>
<td>102 (34.9)</td>
<td>81 (33.2)</td>
<td>$X^2 = 0.18$</td>
<td>.67</td>
</tr>
<tr>
<td>≥4 Lifetime affective episodes (prior to and including intake)</td>
<td>80 (27.4)</td>
<td>72 (29.5)</td>
<td>$X^2 = 0.29$</td>
<td>.59</td>
</tr>
<tr>
<td>Study intake MDE is primary MDE</td>
<td>144 (49.3)</td>
<td>159 (65.2)</td>
<td>$X^2 = 13.59$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severity of study intake MDE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAS for worst period of MDE, t mean (SD)</td>
<td>38.5 (9.9)</td>
<td>38.0 (10.9)</td>
<td>$t_{534} = 0.57$</td>
<td>.57</td>
</tr>
<tr>
<td>Psychotic features</td>
<td>36 (12.3)</td>
<td>28 (11.5)</td>
<td>$X^2 = 0.09$</td>
<td>.76</td>
</tr>
<tr>
<td>Extracted Hamilton Depression score, t mean (SD)</td>
<td>27.4 (6.7)</td>
<td>25.8 (7.2)</td>
<td>$t_{534} = 2.77$</td>
<td>.006</td>
</tr>
<tr>
<td>Duration of study intake MDE, t wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>91 (61-113)</td>
<td>49 (31-65)</td>
<td>$X^2 = 9.76$</td>
<td>.002</td>
</tr>
<tr>
<td>Probability of lasting ≥1 y</td>
<td>.60</td>
<td>.49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GAS, Global Assessment Scale; MDE, major depressive episode.

* Satterthwaite adjustment to df, for unequal group variances.
* For only 290 participants who experienced an MDE with overt irritability.
* The GAS scores measure severity of symptoms and impairment. Scores range from 1 (most severe and impaired) to 100 (superior functioning with no symptoms). A mean score of 38 represents major impairment in several areas, some impairment in reality testing or communication, or at least 1 suicide attempt.

## Chronicity and Severity of Long-term Course
The irritable group had a more chronic and severe long-term course of illness, with a significantly higher mean percentage of follow-up weeks with affective symptoms ($P = .004$), in an affective episode ($P = .003$), or in a major affective episode ($P = .03$).

## Residual Affective Symptoms Between Affective Episodes
By current RDC and DSM-IV-TR definitions, major affective episode remission/recall is reached when an individual either is fully asymptomatic (has no symptoms of the episode) or has only minimal affective symptoms below the threshold for minor depression/dysthymia or hypomania for 8 consecutive weeks. The irritable group had a significantly higher percentage of time with residual minimal affective symptoms between affective episodes ($P = .03$).

## Lifetime Comorbidity
A significantly higher percentage of the irritable group had a lifetime diagnosis of substance abuse disorders ($P < .001$)—either alcoholism ($P < .001$) or drug use disorder ($P = .02$)—and of all anxiety-related disorders (from $P = .001$ to $P = .04$) except obsessive-compulsive disorder ($P = .29$) (Table 3). Rates of other specific RDC disorders were very low in both analysis groups, being significantly higher for the irritable group only with regard to antisocial personality disorder ($P = .005$).

## Psychosocial Impairment
Prior to study intake, the irritable group had significantly greater impairment in global functioning ($P = .002$) and social relationships ($P = .03$) including with spouse/partner ($P < .001$) (Table 4), plus a higher rate of poor occupational and/or school performance since 15 years of age ($P < .001$). During long-term follow-up, the irritable group had significantly worse impairment on the global rating of impairment ($P = .001$) and LIFE-Range of Impaired Functioning Tool composite score ($P < .001$) and in specific areas of work/occupational performance ($P = .04$), household tasks ($P = .009$), and relationship with one's spouse/partner ($P = .03$).

## Quality of Life
Prior to Study Intake
At study intake, CDS participants rated their overall level of satisfaction (contentment, gratification, and feeling that their needs and desires have been fulfilled) for the best 6-month pe-
Overt Irritability/Anger in Unipolar MDEs

Suicidal Ideation and Behavior
There were no significant differences between the 2 groups in suicidal ideation or behavior at study intake or during follow-up, although the irritable group was slightly higher on all measures.

Conversion to a Bipolar Disorder During Follow-up
There was no significant difference between the analysis groups in rates of switching to a bipolar diagnosis during long-term follow-up.

Rates of Bipolar Disorder Among Relatives
The irritable group had a significantly higher percentage of interviewed first-degree relatives with bipolar disorder (P = .02; 95% CI = 1.16-4.57).

Table 2. Affective Illness Course During Long-term Follow-up for Groups Defined by Clinically Significant Symptoms of Overt Irritability During Study Intake Unipolar MDEs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants With Overt Irritability (n = 292)</th>
<th>Participants Without Overt Irritability (n = 244)</th>
<th>Significance Value With df</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First well intervala</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>214</td>
<td>190</td>
<td>( \chi^2 = 1.04^b )</td>
<td>.31</td>
</tr>
<tr>
<td>Median duration (95% CI), wk</td>
<td>144 (116-211)</td>
<td>195 (131-293)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of lasting ≥1 y</td>
<td>.69</td>
<td>.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up period, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>16.9 (10.1)</td>
<td>15.5 (10.6)</td>
<td>( t_{534} = 1.53 )</td>
<td>.13</td>
</tr>
<tr>
<td>Range</td>
<td>0.04-30.00</td>
<td>0.10-31.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With ≥5-y follow-up period</td>
<td>242 (82.9)</td>
<td>194 (79.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With ≥10-y follow-up period</td>
<td>203 (69.5)</td>
<td>150 (61.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With ≥20-y follow-up period</td>
<td>138 (47.3)</td>
<td>105 (43.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective symptoms or in an affective episode</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>262</td>
<td>244</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up, a mean (SD), % of wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With any affective symptoms</td>
<td>60.6 (32.9)</td>
<td>51.3 (34.4)</td>
<td>( .004^d )</td>
<td></td>
</tr>
<tr>
<td>In any affective episode</td>
<td>46.4 (31.7)</td>
<td>38.2 (31.8)</td>
<td>( .003^d )</td>
<td></td>
</tr>
<tr>
<td>In a major affective episode</td>
<td>31.3 (30.0)</td>
<td>25.4 (29.1)</td>
<td>( .03^d )</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic vs residual symptom MDE recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>254</td>
<td>212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between affective episodes with residual affective symptoms during all of follow-up, a mean (SD), % of wk</td>
<td>33.1 (34.8)</td>
<td>26.7 (33.4)</td>
<td>( .03^d )</td>
<td></td>
</tr>
<tr>
<td>MDEs within 15 y after study intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>163</td>
<td>121</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of MDEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.2 (2.8)</td>
<td>4.9 (3.3)</td>
<td>( .21^d )</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>4.0 (1-8)</td>
<td>4.0 (1-18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: MDE, major depressive episode.

a Weeks from remission/recovery from the study intake MDE to start of next affective episode or censored data (from survival analysis).

b Determined using a 2-tailed Wilcoxon rank sum test.

c Data on illness status during follow-up are based on follow-up periods rated “fair” or better in terms of the accuracy of the data (ie, excluding 5.7% of weeks deemed to have “poor” or “very poor” data). To minimize the impact of the study intake MDE, participants with less than 2 years (104 weeks) of “reliable” illness status data were excluded from these analyses.

d Determined using a 2-tailed Wilcoxon rank sum test.

e For participants with any follow-up data when not in any affective episode.

f For participants with at least 15 years of follow-up.

The association of key clinical variables with overt irritability during the study intake MDE remained statistically significant after covarying for each of the 3 available RDC categories of current comorbidity: substance abuse, anxiety disorder, and any substance abuse or other RDC mental disorder (eTable 2 in Supplement). These results indicate that the major findings of our study are not fully explained by the higher rates of comorbid disorders in the irritable group.
eTable 3 in Supplement, owing entirely to a higher rate of type II bipolar disorder (P = .008).

Psychotropic Treatment

The mean (SD) percentage of weeks with any prescribed antidepressant during the study intake MDE was significantly lower for the irritable group than for the nonirritable group: 61.6% (38.9%) vs 68.2% (37.6%) (P = .02, determined by use of the Wilcoxon rank sum test). However, the mean (SD) percentage of weeks receiving a therapeutic level of antidepressant was not significantly different between the irritable group and the nonirritable group: 27.2% (33.0%) vs 32.3% (36.0%) (P = .24, determined by use of the Wilcoxon rank sum test). During the recovery interval following the end of the study intake MDE, the 2 analysis groups did not have significantly different mean percentages of weeks with an antidepressant at any level (P = .29) or at a therapeutic level (P = .48).

Discussion

We have previously reported on the clinical correlates of overt irritability/anger during bipolar MDEs. A second concurrent symptom, psychomotor agitation, was found to be associated with several significant clinical outcomes in the bipolar study, but only with significantly older age and worse depressive severity of study intake unipolar MDEs (eTable 4 in Supplement), leading us to focus the present study on overtly expressed irritability/anger.

To our knowledge, this is the first investigation to examine the association between irritability/anger during unipolar MDEs at study intake and the subsequent long-term course of illness. We found that 292 of 536 participants (54.5%) who experienced a unipolar MDE had symptoms of overtly expressed irritability/anger during their study intake MDE. Although these are not core symptoms for the diagnosis of an MDE, they are present to a clinically significant degree in more than half of the participants. Concurrent anger/irritability was associated with significantly increased depressive severity and a longer duration of the index MDE. We did not find features of atypical depression, as reported by Benazzi and Akiskal and Perlis et al, nor an increased history of suicide attempts or suicidal ideation as reported by Perlis et al. Although the irritable group did not have more MDEs prior to study intake or during follow-up, their study intake MDEs lasted longer, and their prospectively observed course of affective illness was significantly more chronic (more time symptomatic) and severe (more of follow-up in a major affective episode). In addition to a greater symptomatic burden of illness and psychosocial dysfunction, they also had significantly more comorbidities with anxiety and substance use disorders. Using CDs longitudinal data, we were able to extend the findings from prior cross-sectional studies and identify increased long-term chronicity, severity, psychosocial impairment, and comorbidity and lower life satisfaction associated with overt irritability/anger during the study intake MDE. We found no such long-term outcomes in relation to another common characteristic of unipolar MDEs: psychomotor agitation.

The present study provides limited evidence consistent with the hypothesis of underlying bipolarity in patients with MDEs accompanied by overtly expressed irritability/anger. Although we did not find a significantly greater risk of developing hypomania or mania during follow-up, our study participants were significantly younger, had an earlier age at onset of depressive illness, and had significantly more first-degree relatives with bipolar II disorder.
Table 4. Psychosocial Impairment and Quality of Life Prior to Study Intake and During Long-term Follow-up for Groups Defined by Clinically Significant Symptoms of Overt Irritability During Study Intake Unipolar MDE

<table>
<thead>
<tr>
<th>Measure of Psychosocial Impairment or Quality of Life</th>
<th>Participants With Overt Irritability (n = 292)</th>
<th>Participants Without Overt Irritability (n = 244)</th>
<th>Significance Value With df</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment prior to intake, mean (SD) rating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global rating (SADS item 1245)</td>
<td>2.52 (0.91)</td>
<td>2.26 (0.95)</td>
<td>$t_{235} = 3.18$</td>
<td>.002</td>
</tr>
<tr>
<td>Social relationships (SADS item 1242)</td>
<td>3.00 (1.07)</td>
<td>2.80 (0.96)</td>
<td>$t_{235} = 2.17$</td>
<td>.03</td>
</tr>
<tr>
<td>Relationship with spouse/partner (LB item 830)</td>
<td>3.46 (1.08)</td>
<td>2.85 (1.26)</td>
<td>$t_{235} = 4.41$</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Poor or very poor relationship with spouse/partner, No./Total No. (%)</td>
<td>83/164 (50.6)</td>
<td>38/123 (30.9)</td>
<td>$X^2 = 11.20$</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Poor occupational/school performance since age 15 (SADS item 1147), No. (%)</td>
<td>89 (30.5)</td>
<td>44 (18.0)</td>
<td>$X^2 = 11.04$</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Impairment during long-term follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global ratinga</td>
<td></td>
<td></td>
<td>$t_{265} = 3.01$</td>
<td>.003</td>
</tr>
<tr>
<td>No. of participants</td>
<td>256</td>
<td>201</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) rating</td>
<td>2.90 (0.86)</td>
<td>2.65 (0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIFE-RIFT scoreb</td>
<td></td>
<td></td>
<td>$t_{265} = 3.58$</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>No. of participants</td>
<td>256</td>
<td>201</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) rating</td>
<td>11.41 (2.97)</td>
<td>10.41 (2.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workc</td>
<td></td>
<td></td>
<td>$t_{264} = 2.04$</td>
<td>.04</td>
</tr>
<tr>
<td>No. of participants</td>
<td>241</td>
<td>175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) rating</td>
<td>2.64 (1.29)</td>
<td>2.39 (1.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household duties</td>
<td></td>
<td></td>
<td>$t_{261} = 2.64$</td>
<td>.009</td>
</tr>
<tr>
<td>No. of participants</td>
<td>255</td>
<td>198</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) rating</td>
<td>2.40 (0.71)</td>
<td>2.23 (0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relationship with spouse/partnerd</td>
<td></td>
<td></td>
<td>$t_{261} = 2.21$</td>
<td>.03</td>
</tr>
<tr>
<td>No. of participants</td>
<td>171</td>
<td>132</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) rating</td>
<td>2.38 (0.90)</td>
<td>2.15 (0.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life (global life satisfaction)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to study intake</td>
<td></td>
<td></td>
<td>$t_{245} = 2.43$</td>
<td>.02</td>
</tr>
<tr>
<td>No. of participants</td>
<td>256</td>
<td>201</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Mean (SD) rating</td>
<td>2.25 (0.89)</td>
<td>2.05 (0.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During long-term follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>256</td>
<td>201</td>
<td>$t_{265} = 3.22$</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) rating</td>
<td>2.82 (0.74)</td>
<td>2.59 (0.82)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LB, Life Base; LIFE-RIFT, Longitudinal Interval Follow-up Evaluation–Range of impaired Functioning Tool; MDE, major depressive episode; SADS, Schedule for Affective Disorders and Schizophrenia; SLICE, Streamlined Longitudinal Interval Continuation Evaluation.

* Best period in 5 years prior to study intake.

a Ratings are on a 6-point scale from 1 (good functioning in all areas) to 6 (major impairment in several areas). Mean scores for the groups fall between 2 (no more than slight impairment) and 3 (some difficulty in several areas of functioning but generally functioning pretty well).

b Ratings are on a 7-point scale from 1 (superior) to 7 (grossly inadequate). The mean score was 3 (good social relations).

c During the month prior to study intake.

d Ratings are on a 5-point scale with values of 1 (very good), 2 (good), 3 (fair), 4 (poor), and 5 (very poor).

The LIFE-RIFT score is a composite measure of functional impairment composed of the sum of 4 items: (1) the area of worst role impairment (work, household duties, and school); (2) the area of most impairment in relationships (with spouse/partner, children, other relatives, or friends); (3) impairment in recreation and hobbies; and (4) low global life satisfaction. Possible scores range from 4 (best) to 20 (most impaired) in all 4 component areas. A score of 12 would be attained if all 4 components are rated 3 on a 5-point scale, reflecting “mild impairment” in role function and “fair” relationships, recreation, and satisfaction.

e Ratings for the worst week in each month are made based on everything the rater knows about the patient’s social situation, level of functioning, relationships, sex, and satisfaction/contentment. Ratings are on a 5-point scale with values of 1 (very good), 2 (good), 3 (fair to slightly impaired), 4 (poor to moderately impaired), and 5 (very poor to markedly impaired).

f The LIFE-RIFT scale is a composite measure of functional impairment during each month in the follow-up years 3, 4, and 5 (using LIFE-II forms) and during the final month of years from 6 to 31 (using SLICE forms).

g Ratings of global social adjustment for the worst week in each month are based on everything the rater knows about the patient’s social situation, level of functioning, relationships, sex, and satisfaction/contentment. Ratings are on a 5-point scale with values of 1 (very good), 2 (good), 3 (fair to slightly impaired), 4 (poor to moderately impaired), and 5 (very poor to markedly impaired).

h The best period in 5 years prior to study intake.

i Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

j Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

k Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

l Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

m Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

n Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

o Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

p Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

q Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

r Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

s Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

t Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

u Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

v Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

w Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

x Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

y Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).

z Overall rating of the worst week in each month during the final month of follow-up years from 6 to 31 (using SLICE forms).
Meanings and Assessment of Irritability During MDEs

The current literature uses the term irritability in a broad-ranging and often imprecise manner. It has been used to represent inner feelings of annoyance, hostility, or inner psychic tension and as outwardly expressed anger toward people or objects ranging from displeasure or argumentativeness to rage. Despite considerable evidence of high prevalence and an association with important clinical features, and despite being a defining characteristic of manic episodes since 1952, the lack of specificity for the term irritability has been an impediment to effective diagnosis, research, and treatment. Within this variety of meanings, many of which are vaguely defined constructs, we are fortunate that the SADS included an item with a very explicit and precise meaning—overt expression of irritability, annoyance, or anger with clear behavioral descriptors for a 6-point rating of severity. Use of a single symptom item rather than a standardized scale to examine correlates of irritability/anger during MDEs is consistent with other large studies including the Sequenced Treatment Alternatives to Relieve Depression study and the National Comorbidity Survey Replication study. The SADS is unique in assessing overtly expressed anger/irritability not only during the past week but also during the week of the study intake MDE when depressive symptoms were at their most severe (worst week). We defined the irritable group based on their having clinically significant overt irritability/anger during either or both of those weeks.

Analysis based on external expression, rather than subjective feelings alone, is closely aligned with the meaning of irritability as measured by the Present State Examination, in which it is evidenced by outward expressions such as shouting at or quarreling with other people, throwing or breaking objects, or being physically assaultive to others. It is also similar to the meaning of the “Anger-Out” subscale of the State-Trait Anger Expression Inventory-2 of Spielberger. We found this very specific definition of irritability to have a significant association with important clinical characteristics related to long-term illness severity, chronicity, comorbidity, and psychosocial impairment. Those correlates may or may not be associated with other definitions of irritability.

Caveats

Enrollment in the CDS took place from 1978 through 1981. The interim has seen a number of changes in the treatment of MDDs, changes that could potentially affect the course of illness. Furthermore, CDS patients received a diagnosis and were treated at 5 different academic medical centers in the United States. As was customary at that time, the majority (76%) were initially inpatients. This raises the possibility that the results reported herein may not generalize to nonwhite patients or to patients currently seen in private settings, who may have bipolar or schizoaffective MDE or lifetime schizophrenia, different levels of severity, different levels or types of comorbid disorders, or different symptoms or behaviors causing them to present for treatment.

Questions can be raised about the accuracy of follow-up data obtained at 6-month or yearly intervals. A high level of interrater agreement (an intraclass correlation coefficient of ≥0.80) has been demonstrated for assigning Psychiatric Status Ratings and using them to indicate the start and end of affective episodes. The accuracy of psychosocial impairment ratings is supported by their consistency across general measures of functioning (global ratings and Range of Impaired Functioning Tool), as well as specific areas of work, household duties, and relationship with spouse/mate.

The CDS data on the percentage of weeks with any antidepressant treatment, or with antidepressants at a therapeutic level, does not support any conclusion about the effects of specific treatments, which is beyond the scope of our study. Unfortunately, the CDS contains no data on the presence of overt irritability/anger during MDEs that occurred later during follow-up. Thus, we cannot determine whether this is a persistent characteristic, which could help explain the correlation with a more severe and chronic long-term course of illness characterized by greater psychosocial impairment and poorer quality of life.

Implications for Clinical Research and Practice

There is a strong confluence of scientific data from other investigators and the results of our study indicating that concurrent anger/irritability symptoms are important indicators of increased severity, chronicity, and complexity of unipolar major depression. We found that, despite its high prevalence, overt irritability had a low correlation (0.00 to 0.09) with criterion symptoms for MDE in our sample. We interpret those findings as indicating that overt irritability/anger should not be regarded as a core symptom of depression but, rather, as a possible indicator of a clinically important subtype of MDE that needs to be confirmed with further research. Our findings that certain personality characteristics (poor impulse control, high rejection sensitivity, and greater emotional lability), as well as measures of greater psychosocial impairment prior to entering the study and during long-term follow-up, suggest that subthreshold or threshold personality disorders, particularly borderline personality disorder, may predispose a person to outward expressions of irritability/anger. We cannot examine this hypothesis because the CDS did not include a diagnostic assessment of personality disorders other than the RDC diagnosis of antisocial personality disorder, which was significantly higher in the group with overt irritability/anger.

Nor can we evaluate the possible etiological role of posttraumatic stress disorder, which was also not assessed. The results of our study support the possibility that unipolar depression with overt irritability/anger may be a marker for a distinct subtype of unipolar MDD. Correlates such as poor anger management, poor impulse control, increased substance abuse, and greater long-term psychosocial dysfunction raise the question of whether MDEs with irritability/anger arise from a distinct biological substrate. Recent evidence indicates a possible relationship between anger attacks during MDEs and serotonergic dysfunction, including its effects on specific brain regions, as well as subcortical vascular lesions, on particular patterns of cerebral blood flow, and on factors related to vascular morbidity.
of evidence suggesting that symptoms of hostile irritability in severely depressed patients are particularly responsive to selective serotonin reuptake inhibitor antidepressants. Selective serotonin reuptake inhibitors were not yet available during the early years of the CDS. In the present study, we did find that antidepressants of any type were prescribed significantly less during study intake MDEs for the group with overt irritability/anger, despite the fact that the group had significantly more comorbidities, more severe episodes of depression, and greater levels of psychosocial impairment at study intake. Further research is needed to explore how combinations of biological mechanisms, personality vulnerabilities, poor social circumstances, or prior trauma may be involved in the pathogenesis of MDE with overt irritability/anger. Findings from such research could lead to the identification of a distinct subtype of unipolar MDD, along with specific diagnostic tools and more effective treatments.

Results from the present investigation have important clinical implications. First, it is important for clinicians and researchers to identify overt irritability/anger in patients who experience an MDE because such symptoms are a clinical marker for a significantly more complex, chronic, and severe form of MDD. Second, closer clinical monitoring of such patients is warranted. Third, the treatment plan should include specific strategies to address anger management issues, as well as the frequently associated problems of comorbid anxiety disorder, substance abuse disorder, poor impulse control, and psychosocial impairment when these are present. Such an MDD requires thoughtful adjunctive treatment and closer monitoring by the clinician to ameliorate these attendant problematic features.

REFERENCES


