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The Importance of Irritability as a Symptom of Major Depressive Disorder: Results from the National Comorbidity Survey Replication

Maurizio Fava, M.D., **Irving Hwang, M.A.**, **A. John Rush, M.D.**, **Nancy Sampson, B.A.**, **Ellen E. Walters, M.S.**, and **Ronald C. Kessler, Ph.D.**

Department of Psychiatry, Massachusetts General Hospital (Fava); the Departments of Psychiatry and Clinical Sciences, University of Texas Southwestern Medical Center at Dallas (Rush); and the Department of Health Care Policy, Harvard Medical School (Hwang, Sampson, Walters, Kessler)

Abstract

Irritability is a diagnostic symptom of child-adolescent but not adult major depressive disorder (MDD) in both the DSM-IV and ICD-10 systems. We explore the importance of irritability for sub-typing adult DSM-IV MDD in the National Comorbidity Survey Replication (NCS-R), a national US adult household survey. The WHO Composite International Diagnostic Interview (CIDI) was used to assess prevalence of many DSM-IV disorders in the lifetime and in the year before interview (12-month prevalence). MDD was assessed conventionally (i.e., requiring either persistent sadness or loss of interest), but with irritability included as one of the Criterion A symptoms. We also considered the possibility that irritability might be a *diagnostic* symptom of

Address comments to Maurizio Fava, MD, Vice Chair, Department of Psychiatry, Massachusetts General Hospital, Bulfinch 351, 55 Fruit Street, Boston, MA 02114. MFava@Partners.org. Send correspondence to NCS@hcp.med.harvard.edu.

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adult MDD (i.e., detect cases who had neither sad mood nor loss of interest). Twelve-month MDD symptom severity was assessed with the Quick Inventory of Depressive Symptomatology and role impairment with the Sheehan Disability Scale. After excluding bipolar spectrum disorders, irritability during depressive episodes was reported by roughly half of respondents with lifetime DSM-IV MDD. Irritability in the absence of either sad mood or loss of interest, in comparison, was rare. Irritability in MDD was associated with early age-of-onset, lifetime persistence, comorbidity with anxiety and impulse-control disorders, fatigue and self-reproach during episodes, and disability. Irritability was especially common in MDD among respondents in the age range 18–44 and students. Further investigation is warranted of distinct family aggregation, risk factors, and treatment response. Consideration should also be given to including irritability as a non-diagnostic symptom of adult MDD in DSM-V and ICD-11.

Keywords

Epidemiology; Irritability; Major Depressive Disorder (MDD); National Comorbidity Survey Replication (NCS-R); adult

INTRODUCTION

Clinical studies of depressed children and adolescents have shown that the most frequently reported symptom in moderate depression is irritability,[1, 2] which is consistent with the DSM-IV stipulation that irritability is a diagnostic symptom of major depression in children and adolescents (i.e., it detects subjects not detected by sad mood or loss of interest). However, DSM-IV does not include irritability as a symptom of MDD among adults, despite the fact that irritability is commonly found in clinical samples of adults with major depressive disorder (MDD).[3–5] The clinical literature also suggests that irritability might be a meaningful sub-typing variable in MDD, with irritable cases more likely than non-irritable cases to be female, young, unemployed, more severely depressed, lower in functional status and quality of life, and to have a history of at least one suicide attempt.[4] These differences could be of considerable importance, since irritability with anger attacks might be present in more than one-third of patients with MDD,[6–8] although the robustness of these results is difficult to assess due to the fact that irritability was not assessed consistently in these studies.

The above results all come from clinical samples. No study, to our knowledge, has investigated the prevalence or correlates of irritability as a symptom of MDD in a general population sample. The current report presents such results from the National Comorbidity Survey Replication (NCS-R),[9] with the goal of exploring the importance of irritability as a symptomatic sub-typing distinction in a general population sample of people with a lifetime history of MDD.

MATERIALS AND METHODS

Sample

The NCS-R is a nationally representative survey of mental disorders among English-speaking household residents ages 18 and older in the continental US.[9] Interviews were conducted with 9282 respondents between February, 2001 and April, 2003. Verbal informed consent was obtained prior to data collection. Consent was verbal rather than written to maintain consistency with the baseline NCS.[10] The Human Subjects Committees of Harvard Medical School and the University of Michigan both approved the recruitment and consent procedures. Respondents were paid $50 for participation. The response rate was 70.9%. A probability sub-sample of respondents that over-sampled CIDI cases was administered the lifetime non-patient version of the Structured Clinical Interview for DSM-IV (SCID)[11] to validate CIDI diagnoses. These clinical reappraisal study respondents were given a $50 incentive. A probability sub-sample of non-respondents was administered a brief telephone survey and results were used to weight the main sample for non-response bias. Non-respondent survey participants were given a $100 incentive.

The main NCS-R interview was administered in two parts. Part I included a core diagnostic assessment of all respondents (n = 9282). Part II included questions about correlates and additional disorders administered to all Part I respondents who met lifetime criteria for any core disorder plus a roughly one-in-three probability sub-sample of other respondents (n = 5692). A more detailed discussion of NCS-R sampling and weighting procedures is presented elsewhere.[12]

Diagnostic assessment

Diagnoses were based on Version 3.0 of the World Health Organization Composite International Diagnostic Interview (CIDI),[13] a fully structured instrument designed for use by trained lay interviewers who do not have clinical experience. Diagnoses are based on DSM-IV criteria.[14] Diagnostic hierarchy rules were applied in making diagnoses. The core disorders assessed in the survey include mood disorders (major depressive disorder, dysthymia, and bipolar I and II disorder), anxiety disorders (panic disorder, agoraphobia without panic, specific phobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder), substance disorders (alcohol and drug abuse and dependence), and impulse-control disorders (oppositional-defiant disorder, conduct disorder, intermittent explosive disorder). Age-of-onset was assessed with retrospective self-reports at the syndrome level. The CIDI assessment of major depressive episode (MDE) asked about symptoms in the worst lifetime episode and included a number of symptoms in addition to those specified in DSM-IV. One of these was irritability, which was assessed with a simple yes-no question about whether the respondent was “irritable, grouchy, or in a bad mood” most every day during the worst two weeks of the index episode. In retrospect, the decision to assess irritability with only a single question was unfortunate, as we could have evaluated the sensitivity of results to different definitions if multiple items had been used. Furthermore, inclusion of the term “bad mood” in the irritability question might have led to some false positives, to the extent that respondents interpreted this term to mean a sad mood, but our impression from subsequent debriefing

interviews is that this was not a common interpretation in the context of the earlier terms "irritable" and "grouchy". Other symptoms included in the assessment were euphoria, extreme irritability, and several other symptoms of mania-hypomania that were included to distinguish depressive episodes from mixed episodes. CIDI-SCID concordance was found to be good for lifetime diagnoses of MDE ($\kappa = .59$) and excellent for diagnoses of bipolar spectrum disorder, including BP-I, BP-II, and sub-threshold BPD ($\kappa = .94$).

In addition to diagnosing threshold MDD, the CIDI included an assessment of sub-threshold cases, making it possible to calculate how much the estimated prevalence of MDD would increase, if irritability could substitute for sad mood if the latter was not present. Furthermore, in an effort to explore the implications of including irritability as a *core* symptom of MDD (i.e., as a symptom that could substitute for the requirement of either sad mood or loss of interest if neither of the latter was present) among adults rather than only among children and adolescents, a separate assessment of all other symptoms of MDD was made for episodes of irritability in the absence of either depressed mood or loss of interest.

Respondents who met DSM-IV/CIDI criteria lifetime MDD and reported having an episode in the year prior to the interview (12-month MDD) were administered the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR)[15] to assess symptom severity in the worst month of the past year. The QIDS-SR is a fully structured measure that is strongly related both to the clinician-administered IDS-C[16] and to the Hamilton Rating Scale of Depression (HRSD).[17] Transformation rules developed for the QIDS-SR[18] were used to convert scores into clinical severity categories mapped to conventional HRSD ranges of none (i.e., not clinically depressed), mild, moderate, severe, and very severe. These respondents were also administered the Sheehan Disability Scales (SDS)[19] to assess the extent to which depression interfered with functioning in work, household, relationship, and social roles in the worst month of the past year. Responses were scored with a 0–10 visual analogue scale having response options labeled none (0), mild (1–3), moderate (4–6), severe (7–9), and very severe (10).

Analysis methods

Sub-group comparisons were used to study prevalence and correlates of lifetime irritable and non-irritable MDD. Socio-demographic correlates were examined using logistic regression. Age-of-onset distributions were estimated using the two-part actuarial method implemented in SAS.[20] Persistence was examined by calculating means of reported years in any lifetime depressive episode and the proportion of lifetime cases who were in an episode in the past 12 months. Twelve-month clinical severity and severity of role impairment were examined by calculating distributions within the irritable and non-irritable depression subgroups. Lifetime comorbidity was assessed by calculating odds-ratios (ORs) of lifetime irritable and non-irritable MDD with other lifetime DSM-IV/CIDI disorders. Because the NCS-R sample design used weighting and clustering, all statistical analyses were carried out using the Taylor series linearization method,[21] a design-based method implemented in the SUDAAN software system.[22] Significance tests of set of coefficients were made using Wald χ^2 tests based on design-corrected coefficient variance-covariance matrices. Statistical significance was evaluated using two-sided design-based .05 level tests.

RESULT

Prevalence, age-of-onset, and persistence

Of the 19.2% of NCS-R respondents who met lifetime criteria for a major depressive episode (MDE), roughly one-eighth (13.4% of the 19.2%) were classified as having either threshold or sub-threshold bipolar disorder, and another 33.1% reported a lifetime history of core hypomanic symptoms (i.e., a distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting several days or longer with at least one other symptom of hypomania). (Table 1) Roughly equal numbers of the remaining 53.5% of respondents with lifetime MDE reported either the presence (27.7%; n = 489) or absence (25.8%; n = 466) of irritability in their worst lifetime depressive episode, representing 5.3% (irritable MDE) and 5.0% (non-irritable MDE), respectively, of the total NCS-R sample.

The estimated lifetime prevalence (with standard error in parentheses) of irritable MDD would increase by 0.6% (0.1), from 5.3% (0.2) to 5.9% (0.2), if irritability was included as a tenth Criterion A symptom and if diagnosis required sad mood or loss of interest along with a total of at least five of ten Criterion A symptoms (rather than the requirement of at least five of nine in DSM-IV). If irritability was included as a *diagnostic* symptom of adult MDD, so that episodes of irritability in the absence of either sad mood or loss of interest qualified for a diagnosis so long as they were accompanied by at least four other DSM-IV Criterion A symptoms and all other DSM-IV criteria, lifetime prevalence of irritable MDD would increase by another 0.5% (0.1), to 6.4% (0.6). To put this last point in perspective, only 28 additional people out of a sample of 9,282 would meet lifetime criteria for major depression if we allowed irritability to be a diagnostic symptom of adult MDD.

Mean retrospectively reported age-of-onset (AOO) of DSM-IV MDD (i.e., excluding the two kinds of exploratory cases described in the previous paragraph, neither of which meets DSM-IV criteria) was found to be significantly earlier for irritable (26.7 years) than non-irritable (31.3 years) cases ($F_{1,953} = 13.7$, $p < .001$). (Table 2) The shape of the AOO distribution is nonetheless generally consistent for the two sub-types. (Figure 1) The estimated mean number of years in any lifetime episode is also similar for irritable and non-irritable MDD (5.7 vs. 5.1, $F_{1,953} = 0.1$, $p = .75$), although persistence, as indirectly indicated by the ratio of 12-month prevalence to lifetime prevalence, is significantly higher for respondents with irritable (40.3%) than non-irritable (28.8%) MDD ($\chi^2_1 = 9.0$, $p = .004$).

Symptom profiles and episode severity

Tetrachoric factor analysis of the nine DSM-IV Criterion A symptoms of MDD and irritability among NCS-R respondents who endorsed a CIDI diagnostic stem question for lifetime major depression (i.e., a period lasting two weeks or longer when the respondent experienced either sad mood most of the day nearly every day or loss of interest) was carried out. A strong first principal factor (with a .85 cumulative proportion of eigenvalues compared to .20 for the second unrotated principal factor) was found in which the factor loading for irritability (.31) is in the lower end of the inter-quartile range (IQR: 25^{th}-75^{th} percentile) of the factor loadings of the DSM-IV symptoms (IQR: .30–.54). (More detailed results available on request.)

Symptom profiles for the nine DSM-IV Criterion A symptoms in the worst lifetime episode are quite comparable for irritable and non-irritable MDD. (Table 3) Significant differences are limited to fatigue and self-reproach, both of which are significantly more prevalent in irritable than non-irritable MDD. Irritable cases were also marginally more likely than non-irritable cases to report morbid thoughts of death (71.5% vs. 65.5%, $\chi^2_1 = 3.6$, p = .06). More detailed analyses (results available on request) showed that these differences were not due to differences in comorbid DSM-IV/CIDI anxiety, impulse-control, or substance disorders.

The distribution of clinical severity, as defined by the QIDS-SR, does not differ significantly for 12-month irritable vs. non-irritable MDD ($\chi^2_3 = 6.7$, p =.10), with 48.1% of irritable and 45.0% of non-irritable cases classified either severe or very severe. (Table 4) Mean scores on the Sheehan Disability Scales also are quite similar for the two groups, although there is a consistent trend for disability to be slightly higher for irritable than non-irritable MDD. (Table 5)

Socio-demographic correlates

The socio-demographic correlates of irritable MDD are generally similar to those of non-irritable MDD. (Table 6) Both are significantly more common among women than men, with statistically indistinguishable Female:Male odds-ratios (ORs; 1.6 vs. 1.9, $\chi^2_1 = 0.6$, p = .42). Both are inversely related to income and education, although somewhat more strongly so for irritable than non-irritable cases. Both are more prevalent among the previously married than the currently married and among Non-Hispanic Whites than Non-Hispanic Blacks or Hispanics.

There are also notable differences in the associations of irritable and non-irritable MDD with age and age-related socio-demographic variables. Irritable MDD is more prevalent than non-irritable MDD among respondents in the age range 18–44, students, the never married, and respondents in the “other” race-ethnic group (i.e., neither Non-Hispanic White, Non-Hispanic Black, or Hispanic). Non-irritable MDD, in comparison, is more prevalent than irritable MDD among respondents ages 60+. More detailed analyses (results available on request) showed that these differences are not due to differences in comorbid DSM-IV/CIDI anxiety, impulse-control, or substance disorders.

Comorbidity with other DSM-IV disorders

Lifetime comorbidity with other DSM-IV/CIDI disorders was reported by a significantly higher proportion of respondents with irritable (71.3%) than non-irritable (57.9%) MDD ($F_{1, 953} = 6.8$, p = .013), although ORs are consistently greater than 1.0 and generally significant for both sub-types. (Table 7) The ORs of irritable MDD are higher than those of non-irritable MDD with dysthymia and seven of the nine anxiety syndromes assessed in the NCS-R. Four of the latter seven are significant at the .05 level. It is noteworthy that these four – GAD, panic attack, social phobia, and PTSD – include the anxiety disorders with the latest ages of onset. The ORs of irritable MDD are also higher than those of non-irritable MDD with all three of the impulse-control disorders assessed in the core NCS-R: attention-deficit/hyperactivity disorder, oppositional-defiant disorder, and intermittent explosive

disorder. It is noteworthy that all these ORs are statistically significant for irritable MDD, while none is significant for non-irritable MDD. IED might be thought to have an especially strong association with irritability, as the uncontrollable anger attacks of IED could be seen as extreme forms of irritability. Yet only 13.7% of respondents with irritable MDD have a lifetime history of IED. Although this is considerably higher than the 5.5% lifetime prevalence of IED among respondents with non-irritable MDD, it is clear that IED is a minority phenomenon among people with irritable MDD. The ORs of irritable and non-irritable MDD with substance disorders, finally, are generally equivalent.

Treatment

Respondents with lifetime irritable MDD who had a 12-month depressive episode were somewhat more likely than 12-month cases with non-irritable MDD to receive professional treatment for their depression within a year of the interview (64.5% vs. 53.5%, $z = 1.9$, $p = .06$). (Table 8) This difference was especially pronounced among those whose 12-month depression was associated with a very severe Q-IDS-SR score (84.5% vs. 51.4%, $z = 3.6$, $p < .001$). A significantly higher proportion of irritable than non-irritable cases were also treated by a psychiatrist, although this difference was confined to very severe cases (84.5% vs. 43.8%, $z = 4.4$, $p < .001$).

DISCUSSION

The results reported here are limited by the fact that the NCS-R used a fully-structured lay-administered diagnostic interview rather than a semi-structured clinician-administered diagnostic interview. However, the fact that good concordance was found between CIDI diagnoses with blinded SCID clinical diagnoses reduces this concern. In addition, irritability was defined as being “irritable, grouchy, or in a bad mood,” and this definition may be over-inclusive. Another limitation is that irritability was assessed with only a single question for a single worst lifetime episode, possibly leading to more imprecision in the distinction between irritable and non-irritable cases than if the assessment had been made using a more detailed assessment across a number of episodes. The base rate of “irritability” was not assessed in the entire sample, making it impossible to determine whether or not the high prevalence of irritability in MDD is different from the lifetime prevalence of irritability in the general population. However, the fact that irritability second was found to have a significant factor loading with the symptoms of MDE among respondents who endorsed a lifetime history of either dysphoria or anhedonia shows that irritability is associated with the symptoms of DSM-IV major depression. This finding is consistent with clinical evidence that irritability is more common among depressed vs. non-depressed subjects.[23]

The above limitations are likely to lead to the results regarding differences between irritable and non-irritable cases being conservative. An additional limitation, though, might have more complex effects: that respondents were not followed over time or assessed for a family history of bipolar disorder, raising the possibility that at least some of the respondents classified as having irritable MDD might actually be in the bipolar spectrum and might eventually convert to having bipolar disorder. Based on this limitation, the claim that the cases of irritable MDD seen here are non-bipolar should be seen as provisional.

A final noteworthy limitation is that the analysis was carried out exclusively among respondents who met DSM-IV criteria for major depression. This means that respondents with irritable depression were required to have six symptoms compared to five for respondents with non-irritable depression. It could be argued that not allowing irritability to be an alternative to sadness or lack of interest might have introduced a systematic bias toward a relatively more severe form of depression in our analysis. As noted above, though, only 28 additional cases would be classified as having irritable depression if we allowed irritability to be a diagnostic symptom of MDD. This means that any bias introduced in our analysis by requiring respondents with irritable depression to have at least six symptoms would likely be modest. This suspicion was confirmed by replicating all analyses reported above with these 28 respondents added to those considered to have irritable depression. The results were essentially unchanged (results available upon request). The only difference was that the rate of comorbid PTSD in irritable depression (16.6%) was no longer significantly higher than in non-irritable depression (11.3%)..

Within the context of the above limitations, our results provide the first nationally representative US general population prevalence estimates of irritable versus non-irritable MDD. Irritability was found in roughly half the cases of MDD, making it at least as common as a number of the DSM-IV Criterion A symptoms of MDD, including all the reverse vegetative symptoms combined (weight gain, hypersomnia, psychomotor agitation) and psychomotor retardation. This finding is consistent with previous evidence that irritability is more common among depressed than non-depressed subjects.[23] The prevalence of irritability found here is somewhat higher than the 37%–40% irritability prevalence estimates reported in previous studies of depressed outpatients.[4, 5] Recall, though, that these clinical studies considered only symptoms in the current episode whereas we considered symptoms in the worst lifetime episode. In addition, there was no consistency in any of these studies in the methods used to assess irritability.

We excluded respondents with a lifetime history of bipolar (BP) disorder as well as those with a history of either sub-threshold BP disorder[24] or core hypomanic symptoms (i.e., a distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting several days or longer with at least one other symptom of hypomania) in recognition of the fact that depression with anger has been conceptualized by some commentators as a bipolar spectrum disorder.[25] As noted above, the fact that many of the NCS-R respondents are still in the age of risk of onset of BP disorder means that some unknown number of those with irritable MDD might have their diagnoses changed to BP disorder in the future. However, given the very high prevalence of irritability among respondents with lifetime MDD after excluding respondents in the BP spectrum, and taking into consideration that upper bound estimates put lifetime prevalence of BP spectrum disorder at no more than 5–7% of the population,[26, 27] it is very likely that this sort of conversion will occur to a high proportion of the NCS-R respondents classified as having irritable MDD.

Based on the above considerations, our findings challenge the view that irritability in depression is a specific indicator of bipolarity.[28, 29] The findings also raise the question whether the revised DSM and ICD criteria should include irritability as a symptom of non-bipolar depression. Not only did we find that irritability is a common feature of non-bipolar

depression, but we also found that irritability was meaningfully related to a number of significant clinical features. Mean retrospectively reported age-of-onset of MDD is significantly earlier for irritable than non-irritable MDD. Although the shape of the age-of-onset (AOO) distribution is nonetheless generally consistent for the two sub-types, the earlier onset of irritable than non-irritable MDD is consistent with the one, small clinical study of which we are aware that examined this issue.[30] It is unlikely that this is due to differential recall bias, as post hoc analysis shows that the same finding holds when we compare AOO of irritable and non-irritable MDD in sub-samples that are matched on age at interview. It is noteworthy, though, that it has long been known that early AOO of MDE is also often found in BP disorder,[31] again raising a question about the possibility that some cases of irritable MDD are in the BP spectrum.

Another important clinical finding is the significantly greater persistence of irritable than non-irritable MDD, as defined by the proportion of lifetime cases who had a 12-month depressive episode. We are aware of no prior study that has examined this issue. As noted above, the greater persistence of irritable than non-irritable MDD was still present after we controlled for lifetime comorbidity. We also adjusted for differences in AOO, as irritable MDD had an earlier onset than non-irritable MDD, which might explain the more persistent course of irritable MDD, but we found that the significantly higher 12-month/lifetime prevalence ratio of irritable than non-irritable MDD persisted when this control was introduced along with controls for comorbidity. However, retrospectively reported mean number of years with any lifetime episode did not differ significantly for irritable and non-irritable MDD, demonstrating inconsistency in the finding regarding persistence depending on the indicator used to define persistence. As course of illness is a critical clinical feature, more definitive data are needed on differences between irritable and non-irritable MDD in this regard, ideally from prospective studies.

The NCS-R finding that irritability is more prevalent in MDD among respondents in the age range 18–44 and among students is consistent with the finding of a decreasing prevalence of irritability in MDD with age in the STAR*D clinical sample[4] It is conceivable that the comparatively early age-of-onset and young age at interview of respondents with irritable MDE are related to the fact that irritability is such a commonly occurring symptom in child and adolescent depression.[1], [2] Another possibility is that irritability is becoming a more common feature of depressive episodes in recent cohorts.

The finding that severity of illness, as indicated by the QIDS-SR and the Sheehan Disability Scales, did not differ between irritable and non-irritable MDD diverges from the STAR*D finding that patients with irritable MDD had greater illness severity than those with non-irritable MDD.[4] This discrepancy may be due, at least in part, to our finding that people with very severe, irritable MDD were significantly more likely to obtain psychiatric treatment than people with very severe, non-irritable MDD, leading to an over-representation of very severe cases of irritable MDD in specialty treatment samples.

NCS-R respondents with irritable MDD reported a higher prevalence of fatigue, self-reproach and morbid thoughts of death than those with non-irritable MDD. The elevated prevalence of morbid thoughts of death is indirectly consistent with the association between

past history of suicide attempts and irritable MDD in the STAR*D study.[4] The elevated prevalence of self-reproach in NCS-R irritable MDD might be part of the pattern, as self-reproach has been linked to suicidal ideation.[32] It is noteworthy that similar symptom differences were found in the STAR*D sample, but these differences were explained by overall illness severity.[4] It is striking that this is not the case in the NCS-R, as these symptom differences were found despite irritable and non-irritable MDD not differing in overall illness severity. This suggests that symptoms of self-reproach and morbid thoughts of death, and possibly fatigue (which was not elevated among STAR*R patients with irritable MDD) provide some genuine differentiation between irritable and non-irritable MDD. Clearly, though, these differences need to be examined in independent samples controlling for overall illness severity before we can conclude that they are due to more than idiosyncratic features of a single study.

The significantly higher prevalence of comorbid anxiety disorders among people with irritable than non-irritable MDD is in agreement with the observation that MDD outpatients with anxious depression in the STAR*D study were significantly more likely to report irritability than were MDD outpatients without anxious features.[33] As no previous study investigated comorbidity of irritable vs. non-irritable MDD with impulse-control disorders, our finding that impulse-control disorders are comorbid only with irritable MDD is unique. This is potentially important as it is the most dramatic difference we found in the clinical correlates of irritable vs. non-irritable MDD. The association of irritable MDD with impulse-control disorders might account for the thus far unexplored finding in the Epidemiologic Catchment Area Survey that depression was related to violent behavior.[34]

The findings that irritability is a common symptom of MDD and that irritable MDD is associated with distinctive clinical features raises the possibility that the presence of irritability might be a useful MDD sub-typing distinction. Whether this turns out to be the case, though, will require further investigation of differential risk factors, family aggregation, and treatment response. A more detailed investigation of family aggregation of comorbid impulse-control disorders might turn out to be especially illuminating in this regard in light of the unique comorbidity of irritable MDD with impulse-control disorders.

Finally, the association in MDD of irritability with specific symptom clusters and comorbidities may reflect a psychopathological endophenotype that might defy the current DSM-IV nosology and, in fact, cut across DSM-IV clinical entities such as mood and anxiety disorders. A related example of such a cross-cutting distinction exists in the reduction in serotonergic neurotransmission, as suggested by blunted prolactin responses to fenfluramine challenges, reported in patients with both unipolar and bipolar depression,[35] anxiety disorders such as PTSD[36] and personality disorder patients with impulsive aggression.[37] Consistent with these observations, we have found that patients with MDD, irritability and anger attacks had a significantly greater blunting of the prolactin response to fenluramine challenge than MDD patients without irritability and anger attacks.[38] One could hypothesize that this particular endophenotype may share signs of serotonergic dysregulation, in addition to the clinical characteristics that we have identified, although further studies would need to be carried out to assess the specificity and temporal stability of this possibility. .

With regard to differential treatment response, no study has ever investigated whether irritability is a moderator of antidepressant treatment response. However, the fact that MDD patients with irritability and anger attacks have been shown to have distinctive neurobiological features, such as blunting of the prolactin response to fenfluramine challenge[38] and a distinctive pattern of regional cerebral blood flow in the left ventromedial prefrontal cortex and left amygdala during anger induction[39] raises the possibility that there might be distinctive responsiveness to antidepressant treatment. This is an issue that clearly warrants additional investigation in light of the results presented in the current report.

Even before further studies of risk factors and consequences are carried out, though, the results reported here raise the question whether irritability should be included as a symptom of MDD in the revised DSM-V and IDC-11 diagnostic systems. We saw that irritability is as strongly related as other DSM-IV symptoms with the underlying dimension of depression symptomatology in factor analysis. We saw that the prevalence of irritable MDD would be increased by roughly one-fifth (from 5.3% to 6.4% lifetime prevalence), but not dramatically, by including irritability as a core Criterion A symptom of MDD. Thorough evaluation of the extent to which these additional cases would have similar treatment response and correlates to cases that meet current DSM-IV criteria for irritable MDD is beyond the scope of this report. However, the apparent importance of irritability in MDD documented here suggests that clinical studies are needed of the people who would be conferred a diagnosis of MDD if irritability were added as a core symptom in DSM-V and ICD-11.

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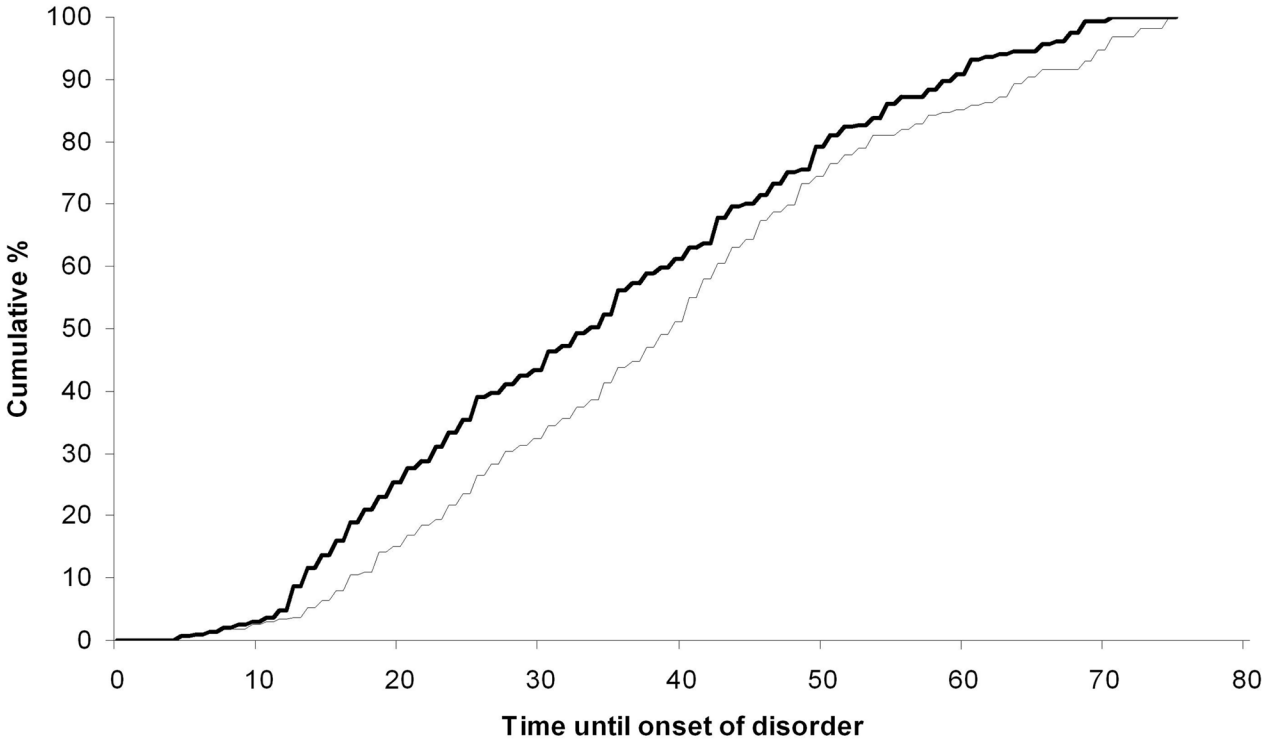

Figure 1.

Age of onset for MDE

— Irritable Depression

— Non-Irritable Depression

Table 1

Disaggregated lifetime prevalence estimates of DSM-IV/CIDI major depressive episode (MDE) in the NCS-R (n=9282)

	Prevalence[1]		Proportion of all MDE	
	%	(se)	%	(se)
Bipolar I-II	1.8	(0.2)	9.2	0.9)
Sub-threshold BPD	0.8	(0.1)	4.2	(0.5)
Core hypomanic symptoms	6.3	(0.3)	33.1	(1.3)
Non-bipolar irritable MDE	5.3	(0.2)	27.7	(1.0)
Non-bipolar non-irritable MDE	5.0	(0.2)	25.8	(1.0)
Total MDE	19.2	(0.5)		
(n)[2]	(9282)		(1829)	

[1] Prevalence estimates are reported on the base of the entire sample. For example, the 1.8% prevalence of MDE with BPD I-II means that 1.8% of the sample both met lifetime criteria for MDE and lifetime criteria for BPD I-II.

[2] The reported sample sizes are unweighted and assessed in the part I sample.

Table 2

Onset and course of irritable and non-irritable DSM-IV/CIDI MDD

	Irritable		Non-irritable MDE		
	Est	**(se)**	**Est**	**(se)**	**F/χ^2**
Mean age of onset	26.7*	(0.7)	31.3	(0.9)	13.7*[1]
Mean years in episode	5.7	(0.5)	5.1	(0.9)	0.1[1]
12-month:Lifetime prevalence	40.3*	(2.7)	28.8	(1.6)	9.0*[2]
(n)[3]	(497)		(480)		

*Significant difference between irritable and non-irritable cases at the .05 level, two-sided test

[1]F test with 1 and 953 degrees of freedom

[2]χ^2 test with 1 degree of freedom

[3]The reported sample sizes are unweighted and assessed in the part I sample.

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Table 3

Symptom profiles[1] of irritable and non-irritable DSM-IV/CIDI MDE

	Irritable		Non-irritable		
	%	(se)	%	(se)	χ^2
Sad mood	99.1	(0.5)	98.6	(0.7)	0.3
Loss of interest	88.2	(2.0)	85.0	(1.8)	1.5
Appetite of weight disturbance					
Appetite/weight gain	18.6	(2.3)	15.8	(2.1)	1.3
Appetite/weight loss	68.9	(2.7)	72.7	(2.5)	1.4
Sleep disturbance					
Hypersomnia	16.7	(1.8)	17.5	(1.5)	0.1
Insomnia	78.0	(2.1)	73.9	(1.7)	2.3
Activity disturbance					
Psychomotor agitation	8.7	(1.6)	7.3	(0.9)	0.5
Psychomotor retardation	41.8	(2.6)	37.2	(2.5)	1.9
Fatigue	89.5*	(1.4)	83.5	(1.9)	11.5*
Self-reproach or guilt	81.3*	(1.5)	65.9	(1.9)	27.8*
Poor concentration or indecisiveness	91.3	(1.4)	87.4	(1.9)	2.3
Morbid thoughts of death	71.5	(2.8)	65.5	(2.4)	3.6
(n)[2]	(497)		(480)		

*Significant difference between irritable and non-irritable MDE at the .05 level, two-sided test

[1]Refers to symptoms in persons with a major depressive episode in the last 12 months.

[2]The reported sample sizes are unweighted and assessed in the part I sample.

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Table 4

Clinical severity (Quick Inventory of Depressive Symptomatology Self-Report) of 12-month[1] irritable and non-irritable DSM-IV/CIDI MDD

	Irritable		Non-irritable	
	%	(se)	%	(se)
Mild	10.4	(2.0)	15.7	(3.0)
Moderate	41.5	(3.7)	39.3	(3.7)
Severe	38.2	(3.4)	28.9	(3.2)
Very severe	9.9	(2.6)	16.1	(2.7)
(n)[2]	(202)		(145)	

*Significance of difference between irritable and non-irritable MDE: $\chi^2_3 = 6.7$, p =.08

[1]12-month MDD is an episode of MDD that occurred at any time within one year of the interview. Severity was assessed for the most severe month in the past year.

[2]The reported sample sizes are unweighted and assessed in the part I sample. Cases are 12-mo cases instead of Lifetime compared to previous tables.

Table 5

Role disability (Mean Sheehan Disability Scale score) of 12-month[1] irritable and non-irritable DSM-IV/CIDI MDE

	Irritable		Non-irritable		
	Mean	**(se)**	**Mean**	**(se)**	**$F_{1,339}$**
Home	5.2	(0.2)	5.0	(0.3)	0.2
Work	4.4	(0.2)	4.0	(0.4)	0.9
Interpersonal	4.7	(0.2)	4.2	(0.3)	3.1
Social	5.6	(0.2)	5.1	(0.3)	2.2
Maximum disability	6.9	(0.2)	6.4	(0.2)	2.7
(n)[2]	(202)		(145)		

*Significant difference between irritable and non-irritable MDE at the .05 level, two-sided test

[1]12-month MDD is an episode of MDD that occurred at any time within one year of the interview. Role disability was assessed for the most severe month in the past year.

[2]The reported sample sizes are unweighted and represents the 12-mo irritable/non-irritable cases in the part I sample.

Table 6

Socio-demographic correlates of lifetime irritable and non-irritable DSM-IV/CIDI MDE

	Irritable				Non-irritable				Irritable: Non-irritable	
	%	(se)	OR	(95% CI)	%	(se)	OR	(95% CI)	χ^2	df
Sex										
Female	7.6	(0.4)	1.6*	(1.3–2.1)	7.3	(0.5)	1.9*	(1.5–2.4)		
Male	4.8	(0.5)	1.0	--	3.9	(0.4)	1.0	--	0.6	1
χ^2_1				14.5*				31.9*		
Age										
18–29	5.7	(0.5)	1.8*	(1.3–2.6)	2.6	(0.4)	0.4*	(0.3–0.6)		
30–44	8.2	(0.7)	2.7*	(1.8–3.9)	5.3	(0.5)	1.0	(0.7–1.3)		
45–59	7.2	(0.6)	2.3*	(1.6–3.4)	8.9	(0.8)	1.6*	(1.2–2.3)		
60+	3.2	(0.5)	1.0	--	5.6	(0.7)	1.0	--	47.8**	3
χ^2_3				30.4*				52.7*		
Education										
0–11	3.4	(0.6)	1.0	--	3.7	(0.7)	1.0	--		
12	6.0	(0.5)	1.8*	(1.2–2.6)	5.2	(0.4)	1.5	(0.9–2.2)		
13–15	6.8	(0.6)	2.1*	(1.4–3.1)	6.0	(0.6)	1.7*	(1.1–2.5)		
16+	7.8	(0.8)	2.4*	(1.6–3.7)	7.5	(0.6)	2.2*	(1.4–3.3)	17.0**	3
χ^2_3				17.7*				26.7*		
Employment status										
Work	6.7	(0.4)	1.0	--	6.1	(0.4)	1.0	--		
Student	6.4	(2.1)	0.9	(0.4–2.1)	0.9	(0.7)	0.1*	(0.0–0.6)		
Homemaker	5.8	(1.1)	0.9	(0.6–1.3)	5.1	(1.1)	0.8	(0.5–1.4)		
Retired	3.6	(0.6)	0.5*	(0.4–0.7)	5.4	(0.9)	0.9	(0.6–1.3)		
Other	7.4	(1.6)	1.1	(0.7–1.8)	5.4	(0.8)	0.9	(0.6–1.2)	7.9	4
χ^2_4				14.8*				8.0		
Family Income[1]										

	Irritable				Non-irritable				Irritable: Non-irritable	
	%	(se)	OR	(95% CI)	%	(se)	OR	(95% CI)	χ^2	df
Low	5.4	(0.6)	1.0	--	4.6	(0.6)	1.0	--		
Low average	5.1	(0.5)	0.9	(0.6–1.3)	4.9	(0.7)	1.1	(0.7–1.4)		
High average	6.5	(0.5)	1.2	(0.7–1.2)	6.2	(0.5)	1.4*	(1.1–2.0)		
High	7.6	(0.7)	1.5	(0.9–1.8)	6.6	(0.5)	1.5*	(1.1–2.1)	0.5	3
χ^2_3				10.2*				14.2*		
Marital status										
Married/cohabitating	5.3	(0.4)	1.0	--	5.6	(0.4)	1.0	--		
Separated/widowed/divorced	8.2	(0.7)	1.6*	(1.3–2.0)	9.1	(1.0)	1.7	(1.3–2.2)		
Never married	6.8	(0.7)	1.3*	(1.0–1.7)	2.9	(0.5)	0.5*	(0.3–0.8)	2.6	2
χ^2_2				21.9*				56.7*		
Race/ethnicity										
Hispanic	3.9	(0.7)	0.5*	(0.4–0.8)	4.5	(0.8)	0.7*	(0.4–1.0)		
Black	3.4	(0.6)	0.5*	(0.3–0.7)	2.2	(0.6)	0.3*	(0.2–0.6)		
Other	8.2	(1.4)	1.1	(0.8–1.6)	4.3	(1.0)	0.6*	(0.4–0.9)		
White	7.0	(0.4)	1.0	--	6.5	(0.4)	1.0	--	4.3	3
χ^2_3				25.5*				19.8*		
Region										
Northeast	6.6	(0.8)	1.0	--	5.6	(0.9)	1.0	--		
South	6.3	(0.7)	0.9	(0.7–1.3)	5.6	(0.6)	1.0	(0.7–1.5)		
Midwest	5.7	(0.5)	0.9	(0.6–1.2)	5.0	(0.6)	0.9	(0.6–1.3)		
West	6.6	(0.6)	1.0	(0.7–1.4)	7.0	(0.7)	1.3	(0.8–1.9)	3.0	3
χ^2_3				1.9				5.6		
(n)[1]	(497)			(7950)	(480)			(7933)		

*Significant at the .05 level, two-sided test

**Significant difference between irritable and non-irritable MDE at the .05 level, two-sided test

[1]The reported sample sizes are unweighted. Prevalences represent the cases with irritable/non-irritable MDE among the demographic categories, while the models are assessed among cases without Lifetime MDE in addition to people with either irritable or non-irritable MDE. There are 7453 cases in the part I sample without Lifetime MDE, and 497/480 cases for irritable/non-irritable respectively. Thus the models for irritable MDE are in a subsample of 7453+497 while for non-irritable MDE, it is 7453+480.

[2]Income was assessed in the part II sample. Models assessed among part II cases without Lifetime MDE and part II cases with irritable/non-irritable MDE.

Table 7

Lifetime comorbidity of irritable and non-irritable DSM-IV/CIDI MDE with other DSM-IV/CIDI disorders

	Irritable				Non-irritable				Irritable: Non-irritable
	%	(se)	OR	(95%CI)	%	(se)	OR	(95% CI)	χ^2_1
Mood disorders									
Dysthymia	17.0	1.6	47.6*	(25.4–89.5)	11.8	2.1	27.3*	(14.1–52.9)	5.6**
Anxiety disorders									
GAD	25.7	1.8	9.2*	(6.9–12.3)	16.4	1.9	4.8*	(3.4–6.7)	15.7**
Panic attack	47.4	2.2	3.0*	(2.4–3.8)	37.8	2.7	2.1*	(1.7–2.7)	8.7**
Panic disorder	9.3	1.1	3.0*	(2.1–4.1)	8.2	1.5	2.6*	(1.6–4.0)	0.2
Social phobia	23.6	1.7	3.4*	(2.8–4.1)	17.0	1.7	2.4*	(1.9–3.1)	6.8**
Specific phobia	20.6	1.7	2.3*	(1.8–3.0)	17.3	1.8	1.9*	(1.5–2.4)	1.7
Agoraphobia	3.5	1.0	2.7*	(1.5–4.9)	3.9	1.0	3.1*	(1.7–5.6)	0.1
Post-traumatic stress disorder	17.7	1.9	4.6*	(3.2–6.5)	11.3	1.4	2.8*	(1.9–4.0)	5.2**
Separation anxiety disorder	5.9	1.0	1.9*	(1.3–2.8)	7.0	2.0	2.6*	(1.6–4.4)	1.1
Obsessive-compulsive disorder	2.2	0.7	7.5*	(2.5–22.7)	0.5	0.5	1.5	(0.2–12.2)	2.3
Any anxiety disorder	54.4	1.7	4.4*	(3.6–5.3)	44.8	2.9	3.1*	(2.5–3.9)	11.1**
Impulse-control disorders									
Attention-deficit/hyperactivity disorder	6.6	1.4	2.4*	(1.3–4.3)	3.6	1.6	1.4	(0.6–3.4)	1.8
Oppositional defiant disorder	7.8	1.2	1.9*	(1.1–3.2)	4.8	1.6	1.5	(0.8–2.5)	0.4
Intermittent explosive disorder	13.7	1.7	2.7*	(2.0–3.8)	5.5	1.1	1.3	(0.8–2.0)	7.0**
Any impulse-control disorder	23.5	1.8	2.8*	(2.1–3.8)	10.4	2.0	1.5	(0.9–2.3)	5.2**
Substance disorders									
Alcohol abuse	16.7	2.8	2.0*	(1.2–3.2)	16.0	2.6	2.1*	(1.4–3.1)	0.0
Alcohol dependence	7.5	1.3	2.3*	(1.4–3.8)	5.7	1.1	1.9*	(1.3–2.9)	0.5
Drug abuse	10.4	1.8	2.0*	(1.2–3.1)	10.0	1.7	2.5*	(1.6–3.9)	0.5
Drug dependence	2.6	0.7	1.4*	(0.7–2.6)	4.9	1.7	3.7*	(1.9–7.3)	3.9**

	Irritable				Non-irritable				Irritable: Non-irritable
	%	(se)	OR	(95%CI)	%	(se)	OR	(95% CI)	χ^2_1
Any substance disorder	18.1	2.8	1.9*	(1.2–2.9)	17.8	2.5	2.1*	(1.5–3.0)	0.1
Any disorder	71.3	2.0	5.2*	(4.1–6.5)	57.9	2.9	3.3*	(2.6–4.2)	6.8**
(n)[1]	(497)			(7950)	(480)			(7933)	

*Significant at the .05 level, two-sided test

**Significant difference between irritable and non-irritable MDE at the .05 level, two-sided test

[1]The reported sample sizes are unweighted. Prevalences represent the cases with the DSM-IV diagnosis among cases with irritable/non-irritable MDE, while the models are assessed among cases without Lifetime MDE in addition to people with either irritable or non-irritable MDE. There are 7453 cases in the part I sample without Lifetime MDE, and 497/480 cases for irritable/non-irritable respectively. Thus the models for irritable MDE are in a subsample of 7453+497 while for non-irritable MDE, it is 7453+480.

[2]The χ^2 values are for the significance of the difference between irritable ands non-irritable MDD

[3]Assessed in the part II sample. Models assessed among part II cases without Lifetime MDE and part II cases with irritable/non-irritable MDE.

[4]Assessed in a random one-third of the part II sample.

[5]Assessed in the part II sample among respondents in the age range 18–44.

Table 8

Treatment of 12-month[1] irritable and non-irritable DSM-IV/CIDI MDE by clinical severity and sector of treatment

	Any treatment[2]				Treatment by a psychiatrist				Sample sizes[3]	
	Irritable		Non-irritable		Irritable		Non-irritable		Irritable	Non-irritable
	%	(se)	%	(se)	%	(se)	%	(se)		
Mild	49.4	(4.6)	51.3	(4.7)	16.5	(6.7)	25.4	(6.1)	(46)	(42)
Moderate	68.5*	(3.5)	53.6	(5.6)	17.4	(4.2)	21.5	(3.6)	(72)	(46)
Severe	66.5	(7.6)	56.7	(6.7)	25.2	(6.2)	26.6	(2.2)	(68)	(35)
Very severe	84.5*	(0.1)	51.4	(8.5)	84.5*	(0.1)	43.8	(9.2)	(15)	(17)
Total	64.5	(3.6)	53.5	(4.5)	24.7	(2.8)	26.8	(3.5)	(201)	(140)
(n)	(201)		(140)		(201)		(140)			

*Significant difference between irritable and non-irritable MDE at the .05 level, two-sided test

[1]12-month MDD is an episode of MDD that occurred at any time within one year of the interview.

[2]Any treatment includes treatment by a psychiatrist, another mental health professional, a general medical professional, a human services professional (e.g., spiritual advisor, social worker in a social services agency), and in the complementary-alternative medical sector (e.g., relaxation therapist, self-help group)

[3]The reported sample sizes are unweighted and assessed in the part II sample.