Agitated "Unipolar" Major Depression: Prevalence, Phenomenology, and Outcome

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Objective: This study aimed to explore how prevalent agitated "unipolar" major depression is, whether it belongs to the bipolar spectrum, and whether it differs from nonagitated "unipolar" major depression with respect to course and outcome.

Method: The study was conducted from January 1, 1978, to December 31, 1996. From 361 patients with major depressive disorder, the authors selected those fulfilling Research Diagnostic Criteria for agitated depression. These 94 patients were compared to 94 randomly recruited patients with nonagitated major depressive disorder regarding demographic and historical features, the clinical characteristics of the index episode, the percentage of time spent in an affective episode during a prospective observation period, and the 5-year outcome. Patients with agitated major depressive disorder who had at least 2 manic/hypomanic symptoms in their index episode were compared to the other patients with agitated major depressive disorder with respect to the same variables.

Results: Patients with agitated major depressive disorder were more likely to receive antipsychotics during their index episode and spent a higher proportion of time in an affective episode during the observation period compared with patients with nonagitated major depressive disorder. The presence of at least 2 manic/hypomanic symptoms in the index episode was associated with a higher rate of family history of bipolar I disorder, a higher score for suicidal thoughts during the episode, a longer duration of the episode, and a higher affective morbidity during the observation period.

Conclusion: The diagnosis of agitated major depressive disorder is not uncommon and has significant therapeutic and prognostic implications. The subgroup of patients with at least 2 manic/hypomanic symptoms may suffer from a mixed state and/or belong to the bipolar spectrum.

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In the last few years, there has been a revival of the interest in agitated depression, a subtype of major depression acknowledged in the Research Diagnostic Criteria (RDC),[1] but not in either the DSM-IV[2] or the ICD-10.[3] It has been reported that this depression subtype is difficult to treat and, contrary to retarded depression, is often refractory to, or even exacerbated by, antidepressant medication.[4–7] Moreover, the subtype has been associated with a higher risk for suicide.[6,8]

Almost all studies dealing with agitated depression have been carried out in samples including both patients with bipolar disorder and patients with major depressive disorder ("unipolar" major depression). The results of the majority of these studies have supported the conceptualization of agitated depression as a mixed state (i.e., a full major depressive syndrome accompanied by subsyndromal mania).[4,5,9,10] However, Swann et al.[11] found that, in patients with RDC-diagnosed agitated depression, the scores for mania were minimal, resembling the scores for depression in patients with nonmixed mania. Furthermore, Schatzberg and DeBattista[7] listed several differential criteria between agitated depression and a mixed episode, including the lack, in the former condition, of grandiosity, decreased need for sleep, external distractibility, increase in goal-directed activities, and increased interest in pleasurable activities.

In a study focusing on agitated bipolar I depression,[12] we found that patients with this diagnosis were consistently not elated or grandiose, but that one fourth of them had the racing thoughts–pressured speech–increased motor activity symptom cluster (corresponding to the factor

2 for mania of Cassidy et al.[13]) and one fourth had the paranoia-aggression-irritability cluster (corresponding to the factor 5 for mania of Cassidy et al.[13]). Compared to patients with nonagitated bipolar I depression, those with agitated depression had a longer duration of their index episode, were more likely to receive antipsychotics during that episode, and spent more time in an affective episode during a prospective observation period. Our conclusion was that the occurrence of agitated depression in bipolar I disorder has significant prognostic and therapeutic implications. However, whether the co-occurrence of one or both of the above-mentioned symptom clusters with a major depressive syndrome makes up a mixed state remains unclear, due to the uncertain specificity for mania of those symptom clusters.

Only one recent study has focused on agitated major depressive disorder (agitated "unipolar" major depression).[14] The study found that patients with this diagnosis, compared to those with nonagitated major depressive disorder, were more likely to have a family history of bipolar disorder and to present at least 3 hypomanic symptoms (the most frequent being distractibility, racing/crowded thoughts, irritable mood, talkativeness, and risky behavior). The conclusion of the authors was that agitated "unipolar" depression should be reconceptualized as a depressive mixed state and should not be treated with antidepressant monotherapy. This conclusion has been supported by another study[15] reporting that patients with "unipolar" depression accompanied by at least 2 manic symptoms were more similar to those with bipolar disorder than to other patients with "unipolar" depression with respect to age at onset, family history of bipolar disorder, and suicidality. In both of these studies, the evaluation was only cross-sectional and the family history of bipolar disorder was assessed by researchers who were aware of the probands' diagnosis.

The present study was conducted in a sample of patients with RDC-diagnosed agitated major depressive disorder, compared with a sample of patients with nonagitated major depressive disorder and one of patients with bipolar I major depression. These patients were assessed both cross-sectionally and throughout a prospective observation period. The family history of bipolar I disorder was assessed by researchers who were not aware of the probands' diagnosis. The study aimed to provide a tentative answer to the following questions: (1) What is the prevalence of the agitated subtype among patients with major depressive disorder seen at a center specialized in the management of mood disorders? (2) Are patients with agitated major depressive disorder more similar to those with bipolar I major depression than to those with nonagitated major depressive disorder with respect to any demographic or historical feature, and in particular, with respect to the age at first psychiatric contact, the rate of a family history of bipolar I disorder, and the frequency of a history of suicide attempts? (3) Is the clinical picture of agitated major depressive disorder different from that of nonagitated major depressive disorder with respect to any feature, besides those included in the definition of the former condition, and in particular, are RDC manic/hypomanic features and suicidality significantly more frequent in agitated than in nonagitated depression? (4) Do patients with agitated major depressive disorder who have at least 2 RDC manic/hypomanic symptoms in their index episode (besides those included in the definition of the disorder) differ significantly from the other patients with agitated major depressive disorder with respect to any demographic or historical feature? (5) Is agitated major depressive disorder treated differently from nonagitated major depressive disorder in clinical practice? (6) Are the course and outcome of agitated major depressive disorder significantly different from those of nonagitated major depressive disorder (and do patients with agitated major depressive disorder who have at least 2 RDC manic/hypomanic symptoms differ from the others in this respect)? (7) Is the pattern of agitated depression consistent over consecutive depressive episodes in patients with major depressive disorder?

METHOD

Subjects and Procedures

The study was carried out at the Center for Affective Disorders of the First Psychiatric Department of Naples University from January 1, 1978, to December 31, 1996, after approval of the protocol by the university's review board. We recruited all consecutive new inpatients and outpatients with an RDC diagnosis of major depressive disorder and a current episode fulfilling the RDC for the agitated subtype who gave written informed consent to participate in the study. The diagnosis was ascertained by the Schedule for Affective Disorders and Schizophrenia (SADS).[16] The RDC for the agitated subtype of major depressive disorder require the presence of at least 2 of the following manifestations of psychomotor agitation (not mere subjective anxiety) for several days during the current episode: pacing; handwringing; unable to sit still; pulling or rubbing on hair, skin, clothing, or other objects; outburst of complaining or shouting; and talking on and on or "can't seem to stop talking." In order to be included in our study, each patient had to score at least 2 on the item agitation of the Comprehensive Psychopathological Rating Scale (CPRS).[17] The definition of this item is consistent with the RDC description: "purposeless motor activity such as hand-wringing, picking at objects and clothes, inability to sit still." For score 2, the CPRS description is "obviously restless; vacant and obtrusive picking at objects; half-rises occasionally"; for score 3, the description is "cannot be persuaded to sit except for brief periods; incessant purposeless wandering."

For each enrolled patient with agitated major depressive disorder, we randomly recruited from the same unit (inpatient or outpatient), during the same year, 1 patient with a diagnosis of major depressive disorder (according to RDC, as ascertained by the SADS) whose index episode did not fulfill the RDC for the agitated subtype and 1 patient with a diagnosis of bipolar I disorder, index episode of major depression (according to RDC, as ascertained by the SADS). The SADS was administered by trained psychiatrists whose interrater reliability had been formally tested and found to be satisfactory.[18]

At the time of recruitment, the following demographic and historical variables were recorded for each patient: sex, age, age at first psychiatric contact, number of previous hospitalizations in a psychiatric ward, history of suicide attempts, history of bipolar I disorder in first-degree relatives (as assessed by the Family History Research Diagnostic Criteria[19]), and co-occurrence of alcoholism or drug abuse (according to the RDC). The symptomatological features of the index episode at its peak were assessed in each patient by the CPRS,[17] which was administered by trained psychiatrists whose interrater reliability had been formally tested and found to be satisfactory.[18] The psychiatrists performing all of the above assessments were not aware of the group to which each patient belonged. We did not require patients to be drug-free at the time of the assessment, because this would have been unfeasible in our setting.

Starting from the time of recruitment, and as long as they remained in contact with the center, all patients were examined every second month, using the CPRS and the version of the SADS for measuring change (SADS-C).[20] Treatment was not under the control of the researchers, but was carefully recorded at each visit. New affective episodes were recorded and classified according to the RDC. Five years after recruitment, all patients, whether or not they were still attending the center, were contacted for a brief interview, during which the Strauss-Carpenter Outcome Scale[21] was administered by a trained psychiatrist who was not aware of the group to which each patient belonged.

Data Analysis

Patients with agitated and nonagitated major depressive disorder and with bipolar I major depression were compared with respect to demographic and historical variables using analysis of variance or the χ^2 test with Yates correction, as appropriate. The χ^2 test with Yates correction was used to compare patients with agitated and nonagitated major depressive disorder with respect to the RDC/SADS profile (percentage of manic/hypomanic and depressive items rated as positive). Analysis of variance was adopted to compare these 2 patient groups with respect to the mean scores on individual CPRS items.

The patients with agitated major depressive disorder who had at least 2 RDC manic/hypomanic symptoms in their index episode (besides those included in the RDC definition of agitated depression, i.e., physical restlessness and increased talkativeness) were compared to the other patients with agitated major depressive disorder with respect to demographic and historical variables using analysis of variance or the χ^2 test with Yates correction, as appropriate. Analysis of variance was adopted to compare these 2 patient subgroups with respect to the mean scores on individual CPRS items.

A univariate logistic regression analysis was performed in all patients with major depressive disorder in order to test whether the presence of each RDC manic/hypomanic symptom during the index episode was associated with a family history of bipolar I disorder. A multiple linear regression analysis was computed in the same patients in order to explore whether the presence of each of the above symptoms was associated with an earlier age at first psychiatric contact.

A multiple linear regression analysis was computed in all patients with major depressive disorder in order to investigate the simultaneous effects of several variables on the time to recovery from the index episode. These variables included the RDC diagnosis of agitated depression, the presence of at least 2 RDC manic/hypomanic symptoms in the index episode (besides those included in the RDC definition of agitated depression), and the number of previous psychiatric hospitalizations. The latter 2 variables were selected because they differentiated patients with agitated major depressive disorder from those with nonagitated major depressive disorder on univariate analyses. Recovery was defined as a period of at least 8 consecutive weeks in which the mood disturbance required by the RDC criterion A for major depression was not present.

A similar analysis was computed in the group of patients with agitated major depressive disorder. The variables included were the presence of at least 2 RDC manic/hypomanic symptoms in the index episode (besides those included in the RDC definition of agitated depression), the score on the CPRS item suicidal thoughts during that episode, and a family history of bipolar I disorder. The latter 2 variables were selected because they differentiated patients with at least 2 RDC manic/hypomanic symptoms from the other patients with agitated major depressive disorder on univariate analyses. Recovery was defined as above.

A multiple linear regression analysis was computed in all patients with major depressive disorder in order to investigate the simultaneous effects of several variables on the percentage of time spent in an affective episode during the prospective observation period (whatever its duration). These variables included the RDC diagnosis of agitated depression, the presence of at least 2 RDC manic/hypomanic symptoms in the index episode (besides those

Table 1. Demographic and Historical Characteristics of Patients With Agitated Major Depressive Disorder, Nonagitated Major Depressive Disorder, and Bipolar I Depression

	Patient Group						Significant Pairwise Comparisons[a]			
	Agitated Major Depressive Disorder (N = 94)		Nonagitated Major Depressive Disorder (N = 94)		Bipolar I Depression (N = 94)		Agitated vs Nonagitated Major Depressive Disorder		Agitated Major Depressive Disorder vs Bipolar I Depression	
Characteristic	Mean	SD	Mean	SD	Mean	SD	F (df = 1,186)	p	F (df = 1,186)	p
Age at recruitment, y	46.8	10.0	45.8	10.2	40.5	10.9			17.0	< .0001
Age at first psychiatric contact, y	34.8	6.1	34.9	6.4	28.1	6.0			57.4	< .0001
No. of hospitalizations prior to index episode	3.7	1.2	2.7	0.8	3.2	1.8	40.1	< .0001	4.7	< .03
	N	%	N	%	N	%	χ^2 (df = 1)	p	χ^2 (df = 1)	p
Sex										
Male	32	34.0	35	37.2	41	43.6				
Female	62	66.0	59	62.8	53	56.4				
History of suicide attempts	26	27.7	17	18.1	25	26.6				
Family history of bipolar I disorder	13	13.8	8	8.5	30	31.9			8.7	< .003
Co-occurrence of alcoholism or drug abuse	4	4.3	5	5.3	6	6.4				

[a]Performed for variables for which a significant difference among groups was found.

included in the RDC definition of agitated depression), and the number of previous psychiatric hospitalizations.

A similar analysis was computed in the group of patients with agitated major depressive disorder. The variables included were the presence of at least 2 RDC manic/hypomanic symptoms in the index episode (besides those included in the RDC definition of agitated depression), the score on the CPRS item suicidal thoughts during that episode, and a family history of bipolar I disorder.

Cohen's κ coefficient was used to explore the consistency between the index episode and each of the depressive episodes recorded during the prospective observation period with respect to the RDC subtype of depression (agitated vs. nonagitated).

A multiple linear regression analysis was performed in all patients with major depressive disorder in order to explore the simultaneous effects of several variables on the global score on the Strauss-Carpenter Outcome Scale at the 5-year follow-up interview. These variables included the RDC diagnosis of agitated depression, the presence of at least 2 RDC manic/hypomanic symptoms in the index episode (besides those included in the RDC definition of agitated depression), and the number of previous psychiatric hospitalizations.

A similar analysis was computed in the group of patients with agitated major depressive disorder. The variables included were the presence of at least 2 RDC manic/hypomanic symptoms in the index episode (besides those included in the RDC definition of agitated depression), the score on the CPRS item suicidal thoughts during that episode, and a family history of bipolar I disorder.

In all analyses, the level of significance was set at $p < .05$, 2-tailed probability.

RESULTS

Of the 361 consecutive new patients with a diagnosis of major depressive disorder seen during the study period, 94 (26.0%) met the RDC for agitated depression. They were 32 men and 62 women, with a mean age at the time of recruitment of 46.8 years (SD = 10.0; range, 24–71 years). Eleven of them were inpatients and 83 were outpatients. The 2 comparison groups consisted of 94 patients with nonagitated major depressive disorder (35 men and 59 women; mean age = 45.8 years, SD = 10.2; range, 24–69 years) and 94 patients with bipolar I major depression (41 men and 53 women; mean age = 40.5 years, SD = 10.9; range, 23–65 years).

Patients with agitated major depressive disorder did not differ significantly from those with nonagitated major depressive disorder with respect to demographic and historical variables, with the exception of the mean number of previous psychiatric hospitalizations, which was significantly higher in the former group. Patients with bipolar I major depression were significantly younger at recruitment and at the time of the first psychiatric contact, and they had a significantly higher rate of family history of bipolar I disorder than both groups of patients with major depressive disorder (Table 1).

The RDC/SADS profile of patients with agitated major depressive disorder differed from that of patients with nonagitated major depressive disorder in several respects. Besides being significantly more likely to present physical restlessness/psychomotor agitation and increased talkativeness (as expected on the basis of the RDC definition of agitated depression), the former patients also displayed irritability, sexual hyperactivity, flight of ideas or racing thoughts, and distractibility with a significantly higher frequency. They also had a significantly higher frequency

Table 2. Manic/Hypomanic and Depressive Items From the Research Diagnostic Criteria Rated as Positive in Patients With Agitated Versus Nonagitated Major Depressive Disorder

	Patient Group				Analysis	
	Agitated Major Depressive Disorder (N = 94)		Nonagitated Major Depressive Disorder (N = 94)			
Item	N	%	N	%	χ^2 (df = 1)	p
Elevated mood	0	0	0	0		
Irritable mood	45	47.9	16	17.0	20.3	< .0001
More active than usual socially or at work	0	0	0	0		
More active than usual sexually	11	11.7	2	2.1	6.7	< .01
Physically restless	94	100.0	6	6.4	164.6	< .0001
More talkative than usual	27	28.7	3	3.2	22.7	< .0001
Flight of ideas or racing thoughts	16	17.0	7	7.4	4.0	.04
Inflated self-esteem	0	0	0	0		
Decreased need for sleep	0	0	0	0		
Distractibility	24	25.5	8	8.5	9.6	< .002
Excessive involvement in activities with potential painful consequences	3	3.2	0	0	3.0	.08
Depressed mood	94	100.0	94	100.0		
Poor appetite or weight loss	57	60.6	54	57.4	0.2	.65
Increased appetite or weight gain	6	6.4	11	11.7	1.6	.20
Sleep difficulty	77	81.9	71	75.5	1.1	.29
Sleeping too much	6	6.4	12	12.8	2.2	.14
Loss of energy or fatigability	57	60.6	69	73.4	3.4	.06
Psychomotor agitation	94	100.0	6	6.4	164.6	< .0001
Psychomotor retardation	9	9.6	72	76.6	85.6	< .0001
Loss of interest in usual activities	73	77.7	91	96.8	15.4	< .0001
Excessive guilt	42	44.7	29	30.9	3.8	.05
Decreased ability to think or concentrate	61	64.9	55	58.5	0.8	.37
Thoughts of death or suicide or suicidal behavior	52	55.3	38	40.4	4.2	.04

of excessive guilt, and suicidal thoughts or behavior (Table 2). Delusional guilt occurred in 19 patients with agitated major depressive disorder (20.2%) and in 8 patients with nonagitated major depressive disorder (8.5%) ($\chi^2 = 5.2$, df = 1, $p < .02$). Mood-incongruent delusions and hallucinations were absent in the patient groups recruited for this study because they are incompatible with a diagnosis of major depression according to RDC (contrary to DSM-IV). No patient with agitated major depressive disorder had elevated mood, increased self-esteem, decreased need for sleep, or increased activity socially or at work, and only 3 of them showed an excessive involvement in activities with potentially painful consequences. Twenty-five patients with agitated major depressive disorder (26.6%) had at least 2 RDC manic/hypomanic symptoms (besides those included in the RDC definition of agitated depression) in their index episode, compared to 9 patients with nonagitated major depressive disorder (9.6%) ($\chi^2 = 9.2$, df = 1, $p < .002$). Forty patients with agitated major depressive disorder (42.6%) did not show any RDC manic/hypomanic symptom except for physical restlessness (required by the RDC definition of agitated depression) during their index episode.

On the CPRS, patients with agitated major depressive disorder had significantly higher mean scores than those with nonagitated major depressive disorder on the items hostility, pressure of speech, flight of ideas, increased sexual interest, inner tension, labile emotional responses, and suicidal thoughts. All patients with agitated major depressive disorder scored 0 on the items elation, ideas of grandeur, and increased energy (Table 3).

The patients with agitated major depressive disorder who had at least 2 RDC manic/hypomanic symptoms in their index episode (besides those included in the RDC definition of agitated depression) were significantly more likely to have a family history of bipolar I disorder than the other patients with agitated major depressive disorder. They also tended to be younger at the time of the first psychiatric contact and to have a more frequent history of suicide attempts, but these differences did not reach a statistically significant level (Table 4).

On the CPRS, the patients with agitated major depressive disorder who had at least 2 RDC manic/hypomanic symptoms (besides those included in the RDC definition of agitated depression) had a significantly higher mean score on the item suicidal thoughts (mean = 0.92, SD = 0.76) compared with the other patients with agitated major depressive disorder (mean = 0.52, SD = 0.53) ($F = 8.1$, df = 1,92; $p < .005$).

The univariate logistic regression analysis performed in all patients with major depressive disorder indicated that the only RDC manic/hypomanic symptom significantly associated with a family history of bipolar I disorder was irritability (exp[B] = 3.1, $p = .05$; model

Table 3. Mean Scores on Selected Items of the Comprehensive Psychopathological Rating Scale in Patients With Agitated Versus Nonagitated Major Depressive Disorder

	Patient Group				Analysis	
	Agitated Major Depressive Disorder (N = 94)		Nonagitated Major Depressive Disorder (N = 94)			
Item	Mean	SD	Mean	SD	F (df = 1,186)	p
Elation	0	0	0	0		
Hostility	0.57	0.70	0.20	0.42	17.8	< .0001
Pressure of speech	0.32	0.53	0.04	0.20	22.1	< .0001
Flight of ideas	0.20	0.48	0.06	0.24	6.2	< .01
Ideas of grandeur	0	0	0	0		
Increased sexual interest	0.12	0.32	0.02	0.14	6.9	< .01
Increased energy	0	0	0	0		
Inner tension	1.47	0.50	0.92	0.49	56.1	< .0001
Labile emotional responses	0.28	0.45	0.05	0.22	18.5	< .0001
Ideas of persecution	0.22	0.47	0.12	0.32	3.3	.07
Suicidal thoughts	0.63	0.62	0.45	0.58	4.2	.04

Table 4. Demographic and Historical Characteristics of Patients With Agitated Major Depressive Disorder Who Had at Least 2 RDC Manic/Hypomanic Symptoms (besides those included in the RDC definition of agitated depression) Compared to the Other Patients With Agitated Major Depressive Disorder

	Patient Group				Analysis	
	Agitated Depression With ≥ 2 RDC Manic/Hypomanic Symptoms (N = 25)		Agitated Depression With < 2 RDC Manic/Hypomanic Symptoms (N = 69)			
Characteristic	Mean	SD	Mean	SD	F (df = 1,92)	p
Age at recruitment, y	46.3	8.2	46.9	10.6	0.07	.80
Age at first psychiatric contact, y	33.5	4.7	35.3	6.5	1.6	.20
No. of hospitalizations prior to index episode	4.0	1.2	3.5	1.2	3.0	.80
	N	%	N	%	χ^2 (df = 1)	p
Sex						
Male	9	36.0	23	33.3	0.06	.80
Female	16	64.0	46	66.7		
History of suicide attempts	10	40.0	16	23.2	2.6	.11
Family history of bipolar disorder	7	28.0	6	8.7	5.7	.02
Co-occurrence of alcoholism or drug abuse	2	8.0	2	2.9	1.2	.28

Abbreviation: RDC = Research Diagnostic Criteria.

$\chi^2 = 18.4$, df = 6, p = .005). The multiple linear regression analysis computed in the same patients showed that no RDC manic/hypomanic symptom was significantly associated with an earlier age at first psychiatric contact.

The multiple linear regression analysis computed in all patients with major depressive disorder showed that a longer time to recovery from the index episode was associated with the presence of at least 2 RDC manic/hypomanic symptoms during that episode ($\beta = 0.15$, $p < .04$) and a higher number of previous psychiatric hospitalizations ($\beta = 0.18$, $p < .02$). The RDC diagnosis of agitated depression did not enter the model ($\beta = 0.07$, $p = .40$) (F of the model = 5.6, df = 3,184; $p < .001$; adjusted $R^2 = 0.07$).

All patients with major depressive disorder received antidepressants during their index episode. In 17 patients with agitated major depressive disorder (18.1%), 1 or more antidepressants were discontinued because of worsening of symptoms; this occurred in 9 patients with nonagitated major depressive disorder (9.6%) ($\chi^2 = 2.84$, df = 1, p = .09). Forty-five patients with agitated major depressive disorder (47.9%) versus 18 of those with nonagitated depression (19.1%) received standard antipsychotic drugs during their index episode ($\chi^2 = 17.31$, df = 1, $p < .0001$). Sixty-eight patients with agitated major depressive disorder (72.3%) versus 49 of those with nonagitated depression (52.1%) received anxiolytics during their index episodes ($\chi^2 = 7.33$, df = 1, p = .007). Ten patients with agitated major depressive disorder (10.6%) versus 15 with nonagitated major depressive disorder (16.0%) received mood stabilizers during their index episode ($\chi^2 = 0.74$, df = 1, p = .39).

The multiple linear regression analysis computed in the group of patients with agitated major depressive disorder revealed that the time to recovery from the index episode was significantly longer in those with at least 2 RDC manic/hypomanic symptoms during that episode ($\beta = 0.33$, $p < .002$). A family history of bipolar I disorder ($\beta = –0.002$; $p = .98$) and the score on the CPRS item suicidal thoughts during the index episode ($\beta = –0.09$, $p = .42$) did not enter the model (F of the model = 3.3, df = 3,90; $p < .02$; adjusted $R^2 = 0.07$).

The patients with at least 2 RDC manic/hypomanic symptoms were significantly more likely to receive standard antipsychotic drugs during their index episode than the other patients with agitated major depressive disorder (68.0% vs. 40.6%; $\chi^2 = 5.47$, df = 1, $p < .02$).

The multiple linear regression analysis computed in all patients with major depressive disorder showed that the percentage of time spent in an affective episode during the prospective observation period was higher in those with agitated depression ($\beta = 0.21$, $p < .005$) and in those with at least 2 RDC manic/hypomanic symptoms in their index episode ($\beta = 0.34$, $p < .0001$), while the number of previous psychiatric hospitalizations did not enter the model ($\beta = –0.01$, $p = .86$) (F of the model = 14.1, df = 3,184; $p < .0001$; adjusted $R^2 = 0.17$).

In the group of patients with agitated major depressive disorder, the multiple linear regression analysis revealed that the percentage of time spent in an affective episode during the prospective observation period was significantly higher among patients with at least 2 RDC manic/hypomanic symptoms in their index episode ($\beta = 0.32$, $p < .003$) and in those with a family history of bipolar I disorder ($\beta = 0.23$, $p < .02$). The score on the CPRS item suicidal thoughts during the index episode did not enter the model ($\beta = –0.08$, $p = .44$) (F of the model = 6.2, df = 3,90; $p < .001$; adjusted $R^2 = 0.14$).

Of the 43 patients with agitated major depressive disorder who had at least 1 further depressive episode during the prospective observation period, 27 (62.8%) had only depressive episodes fulfilling the RDC for the agitated subtype. Of the 37 patients with nonagitated major depression who had at least 1 further depressive episode, 33 (89.2%) had only episodes not fulfilling the RDC for agitated depression. Cohen's κ coefficient measuring the consistency of the diagnosis of agitated depression during the observation period ranged from 0.55 to 0.68. Of the 25 patients with agitated major depressive disorder who had at least 2 RDC manic/hypomanic symptoms during their index episode, 11 had at least 1 further depressive episode during the observation period: 7 had only episodes of agitated depression (63.6%) and 5 had only episodes with at least 2 RDC manic/hypomanic symptoms (45.5%).

The 5-year follow-up interview was possible in 79 patients with agitated major depressive disorder (84.0%) and in 83 of those with nonagitated major depressive disorder (88.3%). Among both patient groups, patients who were lost to follow-up did not differ significantly from the others with respect to baseline clinical features. In the multiple linear regression analysis computed in all patients with major depressive disorder, none of the tested variables was found to influence the 5-year outcome: the RDC diagnosis of agitated depression ($\beta = –0.13$, $p = .12$), the presence of at least 2 RDC manic/hypomanic symptoms ($\beta = –0.10$, $p = .22$), and the number of previous psychiatric hospitalizations ($\beta = 0.08$, $p = .32$) did not enter the model (F of the model = 1.5, df = 3,158; $p = .20$; adjusted $R^2 = 0.10$). In the group of patients with agitated major depressive disorder, none of the tested variables influenced the outcome: the presence of at least 2 RDC manic/hypomanic symptoms ($\beta = –0.21$, $p = .09$), the score on the CPRS item suicidal thoughts ($\beta = 0.13$, $p = .31$), and a family history of bipolar I disorder ($\beta = 0.09$, $p = .32$) did not enter the model (F of the model = 1.2, df = 3,75; adjusted $R^2 = 0.07$).

DISCUSSION

This study confirms that agitated "unipolar" major depression is not a rare condition. In a university center specialized in the management of mood disorders, 26% of patients with major depressive disorder fulfilled the RDC for the agitated subtype. This prevalence is similar to those reported by Spitzer et al.[22] and Koukopoulos et al.[5] (24% and 25%, respectively) and higher than that found by Akiskal et al.[14] in an outpatient sample (19.7%).

The RDC diagnosis of agitated major depressive disorder has significant therapeutic and prognostic implications. Patients with this diagnosis, compared to those with nonagitated major depressive disorder, were more likely to receive standard antipsychotic drugs during the index episode and spent a significantly higher proportion of time in an affective episode during a prospective observation period. These findings are similar to those we reported in a sample of patients with agitated bipolar I depression.[12]

Patients with agitated major depressive disorder did not differ significantly from those with nonagitated major depressive disorder with respect to their age at first psychiatric contact, the rate of family history of bipolar I disorder, and the frequency of a history of suicide attempts. They were not more similar to patients with bipolar I major depression than to the other patients with major depressive disorder with respect to these variables. Moreover, almost one half of the patients with agitated major depressive disorder did not present any RDC manic/hypomanic symptoms during their index episode except for physical restlessness (required by the RDC definition of agitated depression). These findings seem to suggest that agitated "unipolar" depression per se should not be regarded as a mixed state or as part of the bipolar spectrum.

However, the frequency of several RDC manic/hypomanic symptoms—namely, irritability, sexual hyperactivity, flight of ideas or racing thoughts, and distractibility (defined by the RDC as "attention too easily drawn to unimportant or irrelevant external stimuli")—was significantly higher among patients with agitated major depressive disorder than in those with nonagitated major depressive disorder, and as many as 26.6% of patients with the former diagnosis had at least 2 RDC manic/hypomanic symptoms in their index episode (besides those included in the RDC definition of agitated depression). This is in line with the findings of Akiskal et al.[14] and Sato et al.[15] and with our findings in agitated bipolar I depression.[12] The specificity for mania of these symptoms of psychic activation remains questionable. However, patients with at least 2 of these symptoms, compared to the other patients with agitated major depressive disorder, had a significantly higher rate of family history of bipolar I disorder, confirming the results obtained by Akiskal et al.[14] and Sato et al.[15] This finding supports the idea that at least this subgroup of patients with agitated "unipolar" depression may suffer from a mixed state and/or belong to the bipolar spectrum.

The presence of at least 2 RDC manic/hypomanic symptoms in patients with agitated major depressive disorder (in addition to those included in the RDC definition of agitated depression) was associated with a higher score on the CPRS item suicidal thoughts during the index episode, a longer duration of that episode, a higher likelihood to receive standard antipsychotics during it, and a higher affective morbidity during a prospective observation period. These results seem to confirm the notion that the occurrence of manic symptoms in "unipolar" major depression is associated with a greater severity of the syndrome.[23]

Although this study was not designed to address specifically the issue of treatment response, the nonsignificant trend of patients with agitated major depressive disorder to discontinue more frequently antidepressant drugs because of worsening of symptoms is worth noting. This finding seems to partially support the notion that antidepressant medication may not only be insufficient in agitated depression, but even detrimental in some cases.[4,5]

All of the above findings should be replicated in larger patient samples. However, they suggest that agitated depression, in "unipolar" as in bipolar patients, should not be ignored by classification systems and treatment guidelines or algorithms and should become the target of specific drug trials. Moreover, they indicate that the occurrence of multiple manic/hypomanic symptoms in major depressive disorder deserves the same clinical and research attention recently devoted to the occurrence of multiple depressive symptoms in mania.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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