Clinical Factors Associated With Treatment Resistance in Major Depressive Disorder: Results From a European Multicenter Study

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Objectives: Very few studies have investigated clinical features associated with treatment-resistant depression (TRD) defined as failure of at least 2 consecutive antidepressant trials. The primary objective of this multicenter study was to identify specific clinical and demographic factors associated with TRD in a large sample of patients with major depressive episodes that failed to reach response or remission after at least 2 consecutive adequate antidepressant treatments.

Method: A total of 702 patients with DSM-IV major depressive disorder, recruited from January 2000 to February 2004, were included in the analysis. Among them, 346 patients were considered as nonresistant. The remaining 356 patients were considered as resistant, with a 17-item Hamilton Rating Scale for Depression score remaining greater than or equal to 17 after 2 consecutive adequate antidepressant trials. Cox regression models were used to examine the association between individual clinical variables and TRD.

Results: Among the clinical features investigated, 11 variables were found to be associated with TRD. We found anxiety comorbidity ($p < .001$, odds ratio [OR] = 2.6), comorbid panic disorder ($p < .001$, OR = 3.2) and social phobia ($p = .008$, OR = 2.1), personality disorder ($p = .049$, OR = 1.7), suicidal risk ($p = .001$, OR = 2.2), severity ($p = .001$, OR = 1.7), melancholia ($p = .018$, OR = 1.5), a number of hospitalizations > 1 ($p = .003$, OR = 1.6), recurrent episodes ($p = .009$, OR = 1.5), early age at onset ($p = .009$, OR = 2.0), and nonresponse to the first antidepressant received lifetime ($p = .019$, OR = 1.6) to be the factors associated with TRD.

Conclusions: Our findings provide a set of 11 relevant clinical variables associated with treatment resistance in major depressive disorder that can be explored at the clinical level. The statistical model used in this analysis allowed for a hierarchy of these variables (based on the OR) showing that comorbid anxiety disorder is the most powerful clinical factor associated with TRD.

(J Clin Psychiatry 2007;68:1062–1070)

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This study has been supported by an unrestricted grant to the Group for the Study of Resistant Depression (GSRD) by Lundbeck A/S and the Belgian National Fund for Scientific Research (FNRS).

The authors thank Ole Lemming, M.Sc., at Lundbeck Copenhagen for invaluable help in the statistical analyses. The authors also thank Anders Pedersen, M.D., at Lundbeck A/S Copenhagen for advice on the data analyses. Neither Mr. Lemming nor Dr. Pedersen reports any additional financial or other relationship relevant to the subject of the article.

Financial disclosure appears at the end of this article.

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Treatment-resistant depression (TRD) is usually seen as the failure to reach sufficient remission after an adequate treatment. Despite the availability of an increasing number of new antidepressants, it is estimated that TRD occurs in up to 30% to 40% of depressive episodes adequately treated with first-line antidepressant therapy in a psychiatric setting.[1] Patients may experience long periods with depressive symptoms, with modest or insufficient benefit from their treatment. Our limited understanding of this problem makes it almost impossible for the clinician to predict which depressive episode will turn out to be resistant to antidepressant treatment. Treatment outcome has been associated with a number of clinical variables in several studies exploring treatment response to a single antidepressant trial.[2] Recent efforts to conceptualize TRD have led to different definitions that need to be validated before they are used in clinical practice.

Recent meta-analyses have concluded that there is a lack of relevant clinical data to delineate and manage

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TRD, for both pharmacologic and psychological interventions.[3,4] Because of the heterogeneity of TRD, an operational, validated, and systematic definition is still lacking, which limits epidemiologic and therapeutic research.

Thase and Rush[5] proposed a model of staging the different levels of resistance in TRD as follows: stage 1 (failure of at least 1 adequate trial of 1 major class of antidepressant), stage 2 (stage 1 resistance plus failure of an adequate trial of an antidepressant in a different class), stage 3 (stage 2 plus failure of an adequate trial of a tricyclic antidepressant [TCA]), stage 4 (stage 3 plus failure of an adequate trial of a monoamine oxidase inhibitor [MAOI]), and stage 5 (stage 4 plus failure of a course of bilateral electroconvulsive therapy [ECT]). Fava[6] recently proposed an alternative staging model (Massachusetts General Hospital staging method [MGH-S]) generating a continuous variable that represents degrees of resistance from 0 (response to first antidepressant trial). Nonresponse to each subsequent antidepressant trial increases the score by 1 point. Optimization of dose or duration and augmentation/combination of each trial increase the score by 0.5 point. ECT increases the score by 3 points.

We previously proposed an alternative staging method in which depressive episodes are classified as nonresponsive or resistant according to the number and duration of antidepressant trials.[1] Using this principle, any failure is considered as sufficient data to define nonresponder patients. Nonresponse to 2 successive adequate pharmacotherapeutic trials of antidepressants is considered as the first stage of TRD. Staging of TRD corresponds to the number of the following failed adequate antidepressant trials (after 2 trials). Since the above definition applies to acute treatments and does not consider prolonged durations of treatment resistance, we proposed an additional concept, "chronic refractory depression" (CRD). Chronic refractory depression can be defined as a resistant depressive episode lasting at least 12 months despite multiple adequate interventions, including augmentation strategies (Table 1). Considering a mean adequate treatment duration of 6 to 8 weeks, CRD assessed after 1 year corresponds to 6 to 8 consecutive treatment-resistant episodes.

This model does not imply a hierarchy of treatments like that in the Thase and Rush model, in which MAOIs are considered to be more effective than TCAs, while TCAs are considered to be more effective than selective serotonin reuptake inhibitors (SSRIs).

The European Union's Committee for Proprietary Medicinal Products (CPMP) defines TRD as follows: "A patient is considered therapy resistant when consecutive treatments with 2 products of different classes, used for a sufficient length of time at an adequate dose, fail to induce an acceptable effect."[7] "A sufficient length of time" and "adequate dose" are not defined. It is important to point out that the concept of class in these definitions corresponds to the mechanism of action of the product.

Table 1. Staging Method for Treatment-Resistant Depression[a]

(A)	Nonresponder to (specify) TCA, SSRI, MAOI, SNRI, ECT, other
	Nonresponse to 1 adequate antidepressant trial
	Duration of trial: 6–8 weeks
(B)	Treatment-resistant depression
	Resistance to 2 or more adequate antidepressant trials
	Duration of trial:
	TRD1: 12–16 weeks
	TRD2: 18–24 weeks
	TRD3: 24–32 weeks
	TRD4: 30–40 weeks
	TRD5: 36 weeks–1 year
(C)	Chronic refractory depression
	Resistance to several antidepressant trials, including augmentation strategy
	Duration of trial: at least 12 months

[a]Reprinted with permission from Souery et al.[1]
Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SNRI = serotonin and norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Validation of these models is essential before any operational clinical guidelines can be proposed. In a recent study, Petersen et al.[8] investigated empirically the potential predictive value of treatment resistance, ascertained using scores derived from the MGH-S and Thase staging methods, on achieving remission. They found that greater MGH-S scores significantly predicted nonremission and concluded that this observation seems to confirm the validity of this staging model.

Beyond the definition, the identification of factors associated with treatment resistance to antidepressants remains open and needs additional investigations. Numerous studies aimed at identifying predictive factors of treatment response to antidepressants have been performed, but the heterogeneity in the definitions or criteria used for treatment response and the small sample sizes limit replication and prevent definitive conclusions.[9] Some risk factors of nonresponse to a single antidepressant treatment have been proposed. These factors mainly concern the characteristics of the current episode: psychiatric and somatic comorbidities, family history, and psychosocial factors (see references 2, 6, and 10 for review). In addition, most available studies mainly identified clinical factors associated with nonresponse to a single antidepressant treatment, without taking into account multiple treatments and multiple failures in the same episode. Clearly, these factors cannot be used as reliable factors associated with TRD.

Very few studies have investigated clinical features associated with failure of at least 2 consecutive antidepressant trials.[6] The primary objective of this multicenter study was to identify specific clinical and demographic factors associated with TRD in the largest sample published to date focusing on patients with major depressive disorder who failed to reach response after at least 2 consecutive adequate antidepressant treatments. The present

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study focuses on the Souery/CPMP definition of TRD (see Table 1).

METHOD

General Description of the Study and Sample

The aim of the Group for the Study of Resistant Depression (GSRD) was to study methodological issues, operational criteria, and clinical characteristics associated with TRD within the framework of a European multicenter project, "Patterns of Treatment Resistance and Switching Strategies in Unipolar Affective Disorder." Seven European centers took part in this project: Department of Psychiatry, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; Department of Psychiatry, University Hospital Gasthuisberg, Leuven, Belgium; Department of Psychiatry, Istituto Scientifico H San Raffaele, Milan, Italy; Hôpital la Salpetriere, INSERM U302, Paris, France; Sint-Truiden Psychiatric Center, Sint-Truiden, Belgium; Department of Psychiatry, Chaim Sheba Medical Center, Tel-Hashomer, Israel; and Department of General Psychiatry, Medical University Vienna, Vienna, Austria. Recruitment of patients (from January 2000 to February 2004) was based on consecutive ascertainment of depressed inpatients and outpatients in the specialist referral centers involved in the study. Inclusion criteria were (1) meeting criteria for major depressive disorder (DSM-IV criteria) defined as primary (i.e., not secondary to any other Axis I disorder) and (2) at least 1 adequate antidepressant trial received during the current or most recent depressive episode. An antidepressant trial was defined as adequate if (1) it was at least 4 weeks in duration and (2) the dose used was equal to or higher than the lowest dose defined as effective in the product datasheet. Patients with a mood disorder secondary to any primary "nonaffective" psychiatric condition or unwilling to comply with study assessments or not giving informed consent were excluded from the study. Patients were also excluded if they did not receive at least 1 adequate antidepressant treatment during the last depressive episode.

Current and lifetime diagnoses were obtained using a semistructured interview conducted by experienced clinicians using the Mini-International Neuropsychiatric Interview version 5.0.0 Modified for GSRD (MINI).[11] The MINI is a brief, structured interview designed to identify the current and lifetime major Axis I psychiatric disorders from the DSM-IV and ICD-10. The MINI was compared in validation and reliability studies with the Structured Clinical Interview for DSM-III-R (SCID-Patient Version) and has been found to have acceptably high validation and reliability scores.[12–14] A 17-item Hamilton Rating Scale for Depression (HAM-D-17)[15] score was obtained for each patient at inclusion.

Comorbid anxiety disorders, current suicidal risk, and melancholic features were assessed using the MINI. The presence or absence of current or lifetime comorbid anxiety disorder was evaluated by applying diagnostic criteria for each of the anxiety disorders (panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and generalized anxiety disorder). A current suicidal risk is defined in the MINI by the presence of at least 1 of the following suicide-related items: having in the past month thought that it would be better being dead or wishing to die, wanting to harm oneself, thinking about suicide, having a suicide plan, attempting suicide, and ever attempted suicide at least once in the lifetime.

A major depressive episode was defined as severe by clinicians and according to DSM-IV criteria as the presence of several symptoms in excess of those required to make the diagnosis at the worst point in the most recent episode. Each patient was also evaluated using a questionnaire investigating demographic and psychosocial characteristics of the current major depressive episode, including psychiatric and somatic comorbidities, personal and family history of psychiatric disorders, and data on last antidepressant treatments (see Tables 2 and 3).

The assessment of lifetime response to antidepressants was evaluated by psychiatric history and confirmed, when available, using patients' medical records. A specific questionnaire on treatment history was developed for the study. Information was available for both the treatment of past and current episodes with particular attention to the most recent episodes (within the last 12 months). For each patient, a detailed checklist of previous antidepressant treatments was available that included the type of antidepressant, duration of treatment, dose, and the sequence of antidepressants received in case of multiple trials (see Appendix 1). Only those previous treatments for which compliance could be confirmed by the interviewing clinician were considered (or were recorded). Information was also available for any other psychotropic drug taken as comedication during the last episode. The data obtained for the last episode were considered reliable, as shown in a recent study revealing that patients are in general able to recall information regarding trial adequacy and response for treatments received within the last 5 years.[16]

The study protocol was approved by the ethical committees of all participating centers. After a complete description of the study, written informed consent was obtained from all patients.

Definition of Treatment Resistance

An adequate treatment was considered as an antidepressant trial lasting at least 4 weeks at optimal dose of the prescribed antidepressant (at least as high as the lowest dose defined as effective in the product datasheet). These data were used to define treatment resistance in our sample and to assign each patient in 2 different categories. The depressive episode was considered as resistant if the

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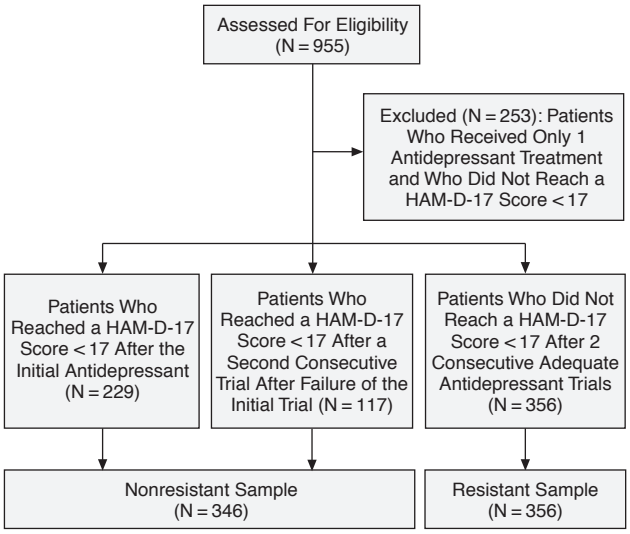
Figure 1. CONSORT Diagram



Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

patient did not reach a HAM-D-17 score < 17 after at least 2 adequate consecutive antidepressant trials administered during the last episode. The depressive episode was defined as nonresistant if a HAM-D-17 score < 17 was reached after a single antidepressant treatment or at the second trial after 1 failure. Resistance status did not require that drugs from 2 different classes of medication be used. Diagnostic evaluations were made blind to the treatment response status (i.e., resistant vs. nonresistant).

Statistical Analyses

Data were analyzed using SPSS version 12.0 software (SPSS Inc.; Chicago, Ill.). Descriptive analyses were used to determine demographic and diagnostic characteristics of the sample. Chi-square and t tests were applied for comparisons between resistant and nonresistant cases. Cox regression models were used to examine the association between individual clinical variables and TRD using resistance/nonresistance as dichotomic dependent variable. All terms associated with TRD with a p value < .05 were then entered into a stepwise Cox regression model, with the p value to enter or to be removed from the model set at .05. The stepwise Cox regression model was applied in order to test independently factors associated with TRD. We hypothesized that some of the variables are likely to be correlated, such as severity and the presence of melancholic features. The stepwise Cox regression model allows for the selection of the most discriminative predictive factors by testing at each step the association between all the variables and by eliminating the less significant ones.

Due to the number of variables investigated and therefore the high number of tests to be done, Bonferroni correction for multiple comparisons was considered as overly conservative, and we decided to include p values < .05 in the presented tables.[17] In addition, the results could be confirmed or refuted by another dataset, for example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.[18]

RESULTS

A total of 955 patients meeting criteria for a major depressive episode and having received at least 4 weeks of adequate antidepressant treatment at optimal dose for the current or most recent episode were assessed (Figure 1). Patients were included during their current episode or after the last episode if treatment response was obtained.

Patients who received only 1 antidepressant treatment and who did not reach a HAM-D-17 score < 17 (N = 253) were not included in the analysis because they did not receive a second treatment, and, therefore, it cannot be known whether or not they would have responded. The remaining 702 subjects were considered for the analysis. A total of 229 patients reached a HAM-D-17 score < 17 after the initial antidepressant, and 117 had a score < 17 after a second consecutive antidepressant trial after failure of the initial trial. These 346 patients were considered as the nonresistant sample (NRS). The remaining 356 patients were considered as resistant since their HAM-D-17 score remained greater than or equal to 17 after 2 consecutive adequate antidepressant trials (resistant sample [RS]).

Demographic and clinical characteristics of the samples are presented in Table 2. Patients from the 2 groups (NRS and RS) did not differ in mean age or gender. Overall, differences in the occupational status were found, with significantly higher frequency of higher executives or employees in the RS (p = .02) and higher frequency of technicians or manual employees in the NRS (p = .02). Patients from the RS were more frequently divorced (p = .02). In addition to the data provided in Table 2, 9.5% of RS and 6.0% of the NRS had a first episode at ≤ 16 years of age (p = .07), and 21.4% of the RS and 20.8% of the NRS experienced their first depressive episode between 17 and 30 years of age. The mean lifetime number of depressive episodes was 3.9 (SD = 5.0) in both groups. In the RS, 50.1% of patients experienced 1 or 2 lifetime depressive episodes (vs. 50.6% in the NRS), including the current episode. In the RS, 24.5% (vs. 28.1% in the NRS) had 3 or 4 episodes, 17.3% (vs. 12%) had 5 to 9 episodes, and 8.1% (vs. 9.3%) experienced more than 9 episodes.

As the last treatment received, patients were given SSRIs (fluoxetine, citalopram, sertraline, fluvoxamine, or paroxetine; 55%), TCAs (clomipramine, desipramine, nortriptyline, amitriptyline, or imipramine; 8%), a serotonin and norepinephrine reuptake inhibitor (venlafaxine, 15%), a norepinephrine reuptake inhibitor (reboxetine,

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Table 2. Demographic and Clinical Characteristics of the Sample of Patients With Major Depressive Disorder

Characteristic	Resistant to Treatment (N = 356)	Nonresistant to Treatment (N = 346)	p Value
Male/female, %	24.7/75.3	30.1/69.9	.1
Caucasian, %	97.2	98	.2
Age, mean (SD), y	50.5 (14.1)	51.5 (14.6)	.1
Educational status, %			
University degree, post–secondary school degree	20.4	22.0	.3
Secondary school superior degree fulfilled	22.2	17.7	.1
Secondary school inferior degree fulfilled	25.7	21.0	.1
Legal school obligations fulfilled	23.1	25.3	.7
Legal school obligations not fulfilled	8.7	14.0	.09
Occupational status, %			
Higher executives, employees	38.1	31.0	.02
Technicians, manual employees	28.6	40.4	.02
Without occupation, invalids, infirms	33.3	28.6	.1
History of physical abuse, %[a]	8.6	10.4	.4
Early parental loss (< 15 years of age), %	12.1	15.5	.3
Immigrants, %	21.2	20.2	.6
Marital status, %			
Single	14.0	16.5	.5
Married	58.7	57.6	.8
Divorced	15.4	9.7	.02
Living together	2.6	5.6	.1
Widow(er)	9.4	10.6	.9
Smoker, %	38.7	34.3	.2
Age at onset (first depressive episode), mean (SD), y	36.8 (15.6)	38.5 (15.6)	.2
No. of depressive episodes, mean (SD)	3.9 (5.0)	3.9 (5.0)	1
Familial history of major depressive disorder, %			
First-degree relatives	44.0	43.0	.8
Second-degree relatives	20.5	18.4	.5
Third-degree relatives	8.8	5.4	.1
Familial history of suicide, %			
Any familial history of suicide	18.0	13.3	.09
Familial history of violent suicide	10.9	10.5	.1
Personal history of suicidal attempt, %			
Any personal history of suicidal attempt	35.2	29.6	.1
Personal history of violent suicidal attempt	9.4	7.2	.7

[a]Assessed during the interview at inclusion in the study without using specific interview.

4%), MAOIs (moclobemide and phenelzine, 1%), a noradrenergic and specific serotonergic antidepressant (mirtazapine, 6%), ECT (1%), and others (mainly mianserin, milnacipran, trazodone, and St. John's wort; 5%). Five percent of the sample was receiving a combination of antidepressants at inclusion, i.e., the association of 2 antidepressants given at adequate dose.

Clinical and treatment characteristics of the current episode are presented in Table 3. Resistant patients were more likely to be hospitalized ($p = .001$) and had higher rates of melancholic features ($p = .02$), anxiety comorbidity ($p < .0001$), and Axis II diagnosis ($p = .04$). Severe intensity of the current episode was more frequently observed in resistant patients, while nonresistant cases experienced more often depressive episodes with moderate intensity ($p = .002$). A current suicidal risk was present in 68.5% of the RS and 49.0% of the NRS ($p < .0001$). A more detailed observation of the intensity of the suicidal risk revealed that the frequencies of moderate to high suicide risk are higher in resistant patients during the current episode ($p = .0001$ and $p < .0001$, respectively). By definition, the number of antidepressant treatments received for the episode is limited to 2 for the nonresistant patients. Among the resistant patients, 18.7% received 3 treatments, 9.2% received 4 treatments, and 4.8% received more than 4 treatments.

A Cox logistic regression model was applied in search of factors associated with resistance. Results are shown in Table 4. In the first step, we examined the relationship between all the variables and TRD. For the comorbidity with anxiety disorders, we found that a lifetime comorbid anxiety disorder, defined as the presence of at least 1 current or lifetime anxiety disorder, was associated with TRD ($p < .001$). Two specific anxiety disorders were significantly associated with TRD: panic disorder with or without agoraphobia ($p < .001$) and social phobia ($p = .008$). Other anxiety disorders (obsessive-compulsive disorder, posttraumatic stress disorder, and generalized anxiety disorder) were not found to be independently associated with TRD. The presence of an Axis II personality disorder was also considered to be associated with TRD ($p = .049$). As for the characteristics of the last or current depressive episode, we found that the presence of a suicidal risk ($p < .001$), severe intensity (as opposed to a moderate intensity, $p = .001$), and melancholic features ($p = .018$) were significantly associated with TRD. Being at suicidal

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Table 3. Clinical Characteristics of the Current Episode

Characteristic	Resistant to Treatment (N = 356)	Nonresistant to Treatment (N = 346)	p Value
Patient status, hospitalized, %	74.4	63.2	.001
Onset of the current episode, %			.4
Abrupt	26.6	29.7	
Slow	73.4	70.3	
Duration of the current episode, mean (SD), wk	53.9 (121)	30.0 (49)	.2
Delay between onset of the episode and initiation of antidepressant treatment, mean (SD), d	69.7 (261)	79.8 (194)	.6
Intensity, %			.002
Moderate	33.4	45.2	
Severe	66.6	54.8	
Melancholic characteristics, %	70.1	61.9	.02
Psychotic characteristics, %	4.8	2.6	.1
Suicide risk (MINI criteria), %	68.5	49.0	< .0001
Low risk	21.9	18.2	.03
Moderate risk	19.4	10.6	.0001
High risk	27.2	13.1	< .0001
Comorbid Axis I diagnoses, %			
Panic disorder (with or without agoraphobia)	24.7	9.1	< .0001
Social phobia	12.1	6.1	.006
Obsessive-compulsive disorder	3.7	2.6	.4
Posttraumatic stress disorder	4.5	2.9	.3
Generalized anxiety disorder	13.5	9.0	.1
Any anxiety disorder	39.3	20.1	< .0001
Alcohol abuse	5.3	5.3	.9
Alcohol dependence	4.8	5.6	.6
Nonalcoholic substance abuse	2.8	0.9	.06
Nonalcoholic substance dependence	3.1	2.0	.4
Anorexia	0.4	0.4	1
Bulimia	2.0	0.7	.2
Axis II diagnosis, %	50.5	37.1	.04
Somatic comorbidity, %			
Any somatic comorbidity	51.4	48.0	.1
Diabetes	15.1	19.1	.2
Thyroid dysfunction	16.1	20.0	.2
No. of antidepressant treatments received for the last episode, %			< .0001
1	0	66.2	
2	67.3	33.8	
3	18.7	0	
4	9.2	0	
> 4	4.8	0	

Abbreviation: MINI = Mini-International Neuropsychiatric Interview.

risk was defined according to the MINI (see above), ranging from the presence of suicidal thoughts to suicide attempt. This definition can be considered as too heterogeneous; therefore, we analyzed item by item the association with TRD and found that each single item was associated with TRD: having in the past month thought that it would be better being dead or wishing to die ($p < .01$), wanting to harm oneself ($p < .01$), thinking about suicide ($p = .01$), having a suicide plan ($p = .02$), attempting suicide ($p = .01$), and having attempted suicide at least once in one's lifetime ($p = .01$).

When considering variables from the personal history, interestingly, nonresponse to a first antidepressant lifetime ($p = .019$) was found to be associated with TRD during the last episode. Early onset of depressive symptoms (before 18 years of age, $p = .009$) and a history of recurrent depressive episodes (as opposed to a single episode, $p = .009$), as well as a number of hospitalizations > 1 ($p = .003$), were also found to be significantly associated with TRD.

These significant variables were then included in a stepwise Cox regression to test independently the factors associated with TRD (Table 3). Four factors were identified as the most discriminative variables associated with TRD: comorbid anxiety disorder ($p < .001$, OR = 4.2), current suicidal risk ($p = .004$, OR = 2.6), melancholic features ($p = .017$, OR = 2.3), and nonresponse to first antidepressant treatment lifetime ($p = .012$, OR = 3.3).

A secondary analysis adjusting for the number of hospitalizations revealed that the characteristics differentiating treatment-resistant from non–treatment-resistant patients remained the same except for melancholia ($p = .22$).

DISCUSSION

This study provides a unique database of patients with major depressive disorder for whom a resistant or nonresistant status can be assigned, based on data collected on the outcome of antidepressant treatments re-

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Table 4. Factors Associated With Treatment Resistance (2-step logistic regression model using nonresistance/resistance as the dependent variable), N = 702[a]

	Initial Univariate Logistic Regression			Second-Step Backward-Elimination Logistic Regression		
Variable	p Value	Odds Ratio	95% CI of Odds Ratio	p Value	Odds Ratio	95% CI of Odds Ratio
Comorbid anxiety disorder	< .001	2.6	1.8 to 3.6	< .0001	4.2	1.9 to 9.3
Comorbid panic disorder	< .001	3.2	2.1 to 5.0			
Current suicidal risk	< .001	2.2	1.6 to 3.0	.004	2.6	1.4 to 5.0
Severe intensity vs moderate intensity	.001	1.7	1.2 to 2.3			
No. of hospitalizations > 1	.003	1.6	1.2 to 2.1			
Social phobia	.008	2.1	1.2 to 3.6			
Recurrent episodes vs single episode	.009	1.5	1.1 to 2.0			
Age at onset before 18 y	.009	2.0	1.2 to 3.3			
Melancholic features	.018	1.5	1.1 to 2.3	.017	2.3	1.2 to 4.7
Nonresponse to first antidepressant treatment lifetime	.019	1.6	1.1 to 2.5	.012	3.3	1.3 to 8.3
Personality disorder (DSM-IV criteria)	.049	1.7	1.0 to 2.9			

[a]All variables from Table 3 were included in the Cox regression. Table 4 includes factors with a p value < .05. Variables are ranked from highest to lowest level of statistical significance on the basis of the univariate analysis.

ceived during the last major depressive episode. Previous studies mainly focused on predictive factors of nonresponse to a single antidepressant trial. The sample size reached within this multicenter effort (702 patients for whom a resistant or nonresistant status can be assigned) allows for a reasonable power in searching for factors associated with TRD. To our knowledge, this is the largest dataset specifically focusing on TRD. The value of our findings relies on the standardization of data collected. Data were specifically collected to document resistance/nonresistance to antidepressant treatment of a major depressive episode.

Among the 702 patients for whom resistant or nonresistant status could be assigned, 356 patients (50.7%) were defined as resistant. The recruitment of our sample from hospitalization settings may explain in part the high degree of severity observed, the high rate of comorbidities, and the relatively poor treatment outcome.

The primary objective of this multicenter study was to identify clinically relevant characteristics associated with TRD in a large sample of patients with major depressive disorder. Among the clinical features investigated in the first step of the Cox regression analysis, 11 variables were found to be associated with TRD. We found anxiety comorbidity (and in particular comorbid panic disorder and social phobia), personality disorder, suicidal risk, severity, melancholia, a number of hospitalizations > 1, recurrent episodes, an early age at onset (< 18 years), and response to the first antidepressant received lifetime to be the factors potentially associated with TRD.

A current or lifetime comorbid anxiety disorder was found in nearly 40% of the RS and only 20% of the NRS. Having a comorbid anxiety disorder increased by 2.6-fold the risk of resistance to antidepressant treatment. Psychiatric comorbidity, including comorbid anxiety and in particular panic disorder, has been associated in several studies with poor treatment outcome of depression and chronicity, particularly in the elderly.[19,20]

Personality disorder was also found to be associated with TRD. This result must be interpreted with caution. This association was found with a borderline p value (p = .049), and no specific questionnaire was used to assess an Axis II disorder; they were defined by the clinician according to DSM-IV criteria.

Suicidal ideation was previously reported as a predictor of nonresponse in single antidepressant trials.[21] We found that suicidal risk during the depressive episode is associated with a 2.2-fold increased risk of resistance. The suicidal risk as assessed by the MINI includes a number of items ranging from suicidal ideation and attempts in the last month to suicidal attempt at least once in the lifetime. While every single item was associated with TRD, it is difficult to differentiate between variables related to the current episode versus those related to previous suicidal behavior.

Pretreatment severity of depressive symptoms has been shown to be a factor of better outcome of antidepressant treatment.[22] In our study, severity was associated with a higher risk of treatment resistance (OR = 1.7). The presence of melancholic features during the episode was also among the clinical variables associated with resistance (OR = 1.5). Recurrent episodes (OR = 1.5) and number of hospitalizations > 1 (OR = 1.6) were also associated with TRD.

Nonresponse to the first antidepressant received in the patient's lifetime increased by 1.6-fold the risk of resistance during the last episode. This result suggests that genetic factors may contribute to treatment response to antidepressants. However, this last observation may be subject to biases in patient recollection of treatment response to the first antidepressant ever received. Finally, an early onset of the disease (< 18 years of age) was associated with TRD (OR = 2.0). This variable may reflect the severity of

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the episode, since it has been shown that early-onset forms of the disease are generally more severe than late-onset forms.[23]

Given the likelihood that several clinical variables are correlated, a stepwise Cox regression model was used to test independently the factors associated with TRD in the first step. From this second-step analysis, 4 variables emerged as being independently correlated to TRD: comorbid anxiety disorder, current suicidal risk, melancholic features, and nonresponse to first antidepressant lifetime. This analysis allowed us to test interactions between the first 11 variables and to identify the most discriminative ones.

There are several limitations in our study. Retrospective assessment represents one of the limitations; however, data were collected during the last episode, which lessens the risk of recollection biases, in particular on treatment response.[16] Treatment adequacy, in our study, was defined as having received at least 4 weeks of the antidepressant at the adequate dose. This duration may be considered insufficient to ascertain a lack of response; however, this time frame is consistent with usual clinical practice. The HAM-D-17 scores were only available at inclusion, i.e., after at least 4 weeks of adequate treatment. Patients were recruited from specialized units for mood disorders and may not be representative of the depressed patients in the general population. Finally, some clinical characteristics having been assessed at inclusion may not have been present at the early stages of the depressive episode. Current suicidal risk mainly reflects suicidal-related items occurring during the last month only. The same observation is true for severity and melancholia. Comorbid anxiety disorder and response to the first antidepressant treatment received lifetime represent the only associated factors to be considered as "enduring features" of TRD. Prospective studies, capturing clinical characteristics at each stage of the depressive episode and the antidepressant sequence, are clearly needed to confirm our results.

In conclusion, our findings provide a set of 11 relevant clinical variables associated with treatment resistance in major depressive disorder, most of which are related to severity. The statistical model used in this analysis allowed for a hierarchy of these variables (based on the OR) showing that comorbid anxiety disorder is the most powerful factor associated with TRD. The exact link between comorbid anxiety and TRD is not clear and deserves further studies. At a therapeutic level, these findings should be replicated in prospective controlled trials designed to study the efficacy of novel treatment strategies in resistant depression. Besides the identification of demographic and clinical factors associated with TRD, future research should also investigate relevant genetic polymorphisms and apply new molecular technologies such as gene expression and proteomics. This may further contribute to clinical and genetic characterization of the subphenotype of TRD.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Financial disclosure: Dr. Demyttenaere has received honoraria from and is a member of the speakers/advisory boards of Lundbeck, Boehringer-Ingelheim, Eli Lilly, and Wyeth. Dr. Kasper has received grant/research support from Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmithKline, Organon, and Servier; is a consultant for and a member of the advisory boards of AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Lundbeck, Pfizer, Organon, Janssen, and Novartis; and is a member of the speakers bureaus of AstraZeneca, Eli Lilly, Lundbeck, and Janssen. Dr. Lecrubier has received honoraria from Pierre Fabre, Lundbeck, Servier, and Pfizer and is a member of the speakers/advisory boards of Eli Lilly, Sanofi, and Novartis. Dr. Montgomery is a consultant to AstraZeneca, Lundbeck, Servier, and Wyeth. Drs. Souery, Oswald, Massat, Bailer, Bollen, Serretti, Zohar, and Mendlewicz report no financial or other relationship relevant to the subject of this article.

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Appendix 1. Checklist for Antidepressant Treatment History[a]

Name of Medication	Daily Dose (mg)	Date of Onset of Treatment (dd/mm/yyyy)	Date of End of Treatment (dd/mm/yyyy)	Reason for Discontinuation	Prescribed for Current or Past Episode
1)					
2)					
3)					
4)					
5)					
6)					
7)					

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