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Original article

Features and pharmacotherapy of treatment-resistant depression: an observational study on hospitalized patients

Gabriele Di Salvo[1], Francesco Cuniberti[1], Matteo Bianco[1], Donatella Ramello[2], Giuseppe Maina[1,2], Gianluca Rosso[1,2]

[1] Department of Neurosciences 'Rita Levi Montalcini', University of Turin, Italy; [2] San Luigi Gonzaga University Hospital of Orbassano (TO), Italy

SUMMARY

Objectives

Treatment-resistant depression (TRD) is a complex and debilitating condition with heavily impacting consequences on healthcare and socio-economic system. The overall picture of TRD still appears conflicting and fragmentary and most studies were conducted on outpatients only.

Aim of this study was to investigate the characteristics of real-world inpatients with TRD in order to provide useful information in daily clinical practice and identify any specific feature of this population.

Methods

We retrospectively examined clinical charts of 250 MDD inpatients, excluding subjects with any type of bipolar disorder. Patients were grouped in two sub-samples, TRD and non-TRD (nTRD); socio-demographic and clinical characteristics were compared between the two subgroups. Furthermore, therapeutic strategies adopted in TRD patients were analysed. Comparisons were performed by using Pearson's χ^2 test with Yates' correction for categorical variables and independent-samples t-test for continuous variables.

Results

The prevalence of TRD in our sample was 32.4%. Compared to nTRD subjects, TRD inpatients were significantly older, while unexpectedly other socio-demographic factors, such as lower educational level and unemployment, did not result associated to TRD. Concerning clinical features, TRD subjects had longer duration of illness, more lifetime depressive episodes, older age at first admission and higher rate of family history for mood disorders and for suicide. They also showed greater severity of the current episode, less comorbid psychiatric disorders and more medical conditions. The lack of correlation between suicidality and TRD was an unexpected result. At discharge, TRD was more related to polypharmacy with higher number of psychotropic drugs in particular; add-on was the most frequent strategy (48.1%) and the atypical antipsychotics (quetiapine above all) were the most frequent add-on medications (68.8%).

Conclusions

We observed several peculiar features of TRD in hospitalized patients that have not been described previously. Further research is awaited to investigate such relationships and help detecting valid therapeutic strategies in inpatients.

Key words: major depressive disorder, treatment-resistant depression, inpatients, suicide, treatment strategies

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Correspondence
Giuseppe Maina
Department of Neurosciences 'Rita Levi Montalcini', University of Turin, via Cherasco 15, 10126 Turin, Italy. Tel.: +39 011 9026517.
Fax: +39 011 9026595
E-mail: giuseppe.maina@unito.it

Conflict of interest
The Authors declare no conflict of interest

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Introduction

Over recent years, Major depressive disorder (MDD) has held great importance in public health due to its increase in both prevalence and consequent disability rate [1]. According to the World Health Organization, it is estimated that by 2030 MDD will have become the leading cause of disability worldwide [2].

Despite such considerable impact of depression, there is still lack of consistently effective medication, as only a few amount of patients manage to achieve full remission with currently available pharmacological treatments [3,4]. Among those who show initial response, up to 50% maintain residual symptoms with high risk of relapse and progression to chronicity [5,6]. Moreover, around 30-40% of patients show no response to first-line treatments and more than 50% do not improve after prescription of a second different antidepressant (AD) [7], thus presenting signs of a resistant disease.

Lack of consensus exists about the concept of treatment-resistant depression (TRD) [8]. A widely used practical criterion for TRD is a minimum of two prior treatment failures and confirmation of prior adequate dose and duration of treatment [9].

However, TRD is a complex and debilitating condition with heavily impacting consequences on healthcare and socio-economic system [10]. Crown and colleagues found that TRD patients present twice the probability of hospital admission, with overall average costs up to six times higher compared to patients with non-TRD [11].

In the recent past a vast literature has deepened socio-demographic and clinical factors related to TRD. The impact of age in failure to respond to AD medication has been broadly investigated, with mixed results [12]: although the majority of studies did not show significant correlation between age and unresponsiveness to treatment, a few found that older age might be associated with lower response to ADs [13]; gender did not seem to be related to responsiveness to treatment [14,15] nor with remission rate[16]. Other variables such as occupation, poor level of education and being divorced or widower were detected as possible predictive factors of TRD [15,17-20].

Concerning clinical variables, age at onset [19,21], severity of depressive symptoms [15,19,22], psychotic and anxiety features [19], number of lifetime depressive episodes [14] and family history for psychiatric disorders including bipolar disorder and suicide[17,18,19] did not appear significantly associated with lack of response to antidepressants. Conversely, melancholic symptoms showed a significant association with lower response [18] as well as length of major depressive episode (MDE) [16,19] and lifetime hospitalization rate [17,18]. Suicide attempt (current) and history of multiple suicide attempts suggested lower response rate to therapies [13,18]; furthermore, existing studies indicated that TRD presents a three-fold higher lifetime suicide attempt rate (17% in TRD vs 6% in nTRD) [22]. Lastly, evidence concerning the role of comorbid disorders showed mixed results: anxiety and substance use disorders seemed to be associated with higher treatment resistance in most studies [16,18], while relationship between TRD and personality disorders was controversial [23,24]; medical conditions were identified as a risk factor for TRD [25] with special reference to thyroid diseases and subclinical hypothyroidism in particular [26].

In light of these findings, the overall picture of TRD still appears conflicting and fragmentary. Furthermore, although TRD patients present twice the probability of hospital admission, with overall average costs up to six times higher compared to patients with non-TRD [11], most studies were conducted on outpatients only [9].

Therefore, aim of this study was to investigate the characteristics of real-world inpatients with TRD in order to provide useful information in daily clinical practice and identify any specific feature of this population.

Materials and methods

Study design and patients

This is an independent observational study with retrospective design.

Clinical charts of 250 patients admitted to the Psychiatric Inpatient Unit of San Luigi Gonzaga Hospital of Orbassano (Turin, Italy) with principal diagnosis of MDD (DSM-5) from January 2016 to December 2018 were reviewed by residents in psychiatry supervised by senior psychiatrists with several years of clinical experience in diagnosis and treatment of depression. Particular attention was paid to the exclusion of all patients with any subtype of bipolar disorder, including bipolar disorder NOS or patients with soft bipolar spectrum.

The present analysis is part of an independent observational study on clinical features of mood disorders which has been reviewed and approved by the local Ethical Committee.

Assessment and procedures

Patients were grouped in two sub-samples, TRD and non-TRD (nTRD), according to whether or not they presented a TRD according to the operational definition, which requires a minimum of two prior treatment failures and confirmation of prior adequate dose and duration [9]. Any case of pseudo-resistance that emerged through detailed examination of clinical charts (e.g. patients who have responded by simply increasing the dosage of the antidepressant compound at admission) was included in nTRD subgroup.

Clinical features examined in our study included:

- psychiatric history of MDD: age at onset, number of lifetime episodes, duration of illness;
- psychiatric family history (with particular regard to mood disorders);
- current episode features: symptoms and severity;
- hospitalization details: length, type of discharge;
- suicidality: current and lifetime suicide attempt rate;

- psychiatric and medical comorbidities;
- AD treatment during the current major depressive episode (MDE) before hospital admission;
- psychiatric and non-psychiatric treatment at discharge.

Furthermore, therapeutic strategies adopted in TRD patients during the hospital stay were analysed, grouping them as follows: (a) switch to other AD belonging to either the same or different pharmaceutical category; (b) combination with a second AD; (c) add-on of a drug not classified as antidepressant to current AD medication (augmentation strategy) [27,28].

Optimization strategy was not considered since patients who were prescribed low AD doses before admission and who showed response to dose increase of the same AD during hospitalization were included in the non-TRD group.

Statistical analysis

Socio-demographic and clinical features of the patients were summarized as mean and standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables.

Comparison between socio-demographic and clinical features of the two groups was performed by using Pearson's χ^2 test with Yates' correction for categorical variables and independent-samples t-test for continuous variables.

All statistical analyses were performed by SPSS software version 26.0.

Results

Two-hundred and fifty clinical charts of inpatients admitted with principal diagnosis of MDD (according to the DSM-5 criteria) were analysed. One-hundred twenty-six patients (50.4%) were female, 124 (49.6%) were male. Eighty-one patients (32.4%) fulfilled the criteria for TRD. Socio-demographic and clinical characteristics of the total sample and differences between TRD and nTRD subjects are given in Table I.

TRD patients were significantly older than nTRD patients (years, TRD 55.3 ± 14.8 *vs* nTRD 48.5 ± 16.3, p = 0.002). There were no significant differences noticed either in gender or in educational, marital and occupational status.

Regarding clinical features, the following results were found:

- psychiatric history: subjects diagnosed with TRD had longer duration of illness (TRD 19.6 ± 15.8 *vs* nTRD 11.9 ± 14.0: p < 0.001), more lifetime depressive episodes (TRD 3.2 ± 1.6 *vs* nTRD 2.6 ± 1.6: p = 0.003) and older age at first admission (years, TRD 44.6 ± 14.7 *vs* nTRD 41.8 ± 17.4: p = 0.027);
- psychiatric family history: TRD patients had higher rate of positive psychiatric family history in I and II grade relatives (TRD 54.3% *vs* nTRD 40.8%: p = 0.045), in particular for suicide (TRD 14.8% *vs* nTRD 4.1%: p = 0.003) and mood disorders (TRD 50.6% *vs* nTRD 28.4%: p = 0.001), although no significant difference was found for bipolar disorder (TRD 0.0% *vs* nTRD 3.0%: p = 0.118);
- current episode features: subjects with TRD showed higher rate of melancholic features (TRD 12.3% *vs* nTRD 3.6%, p = 0.008) and greater severity of the current episode (TRD 42.0% *vs* nTRD 28.4%: p = 0.032);
- hospitalization details: no difference was found in length of hospitalization (days, TRD 8.9 ± 4.8 *vs* nTRD 7.8 ± 6.0: p = 0.161) and type of discharge (e.g. discharge at home, TRD 69.1% *vs* nTRD 75.7%: p = 0.268);
- suicidality: neither current (TRD 16.0% *vs* nTRD 21.0%: p = 0.328) nor lifetime (TRD 25.9% *vs* nTRD 27.8%: p = 0.754) suicide attempt rate was found to be significantly higher in TRD patients;
- psychiatric comorbidities: patients with TRD showed lower rate of psychiatric comorbidities (TRD 39.5% *vs* nTRD 53.8%: p = 0.034). Notwithstanding, no statistically significant correlation was noticed between TRD and specific comorbid disorders, such as alcohol/drug use disorder (TRD 14.8% *vs* nTRD 20.1%: p = 0.311), personality disorders (TRD 22.2% *vs* nTRD 16.6: p = 0.280), anxiety disorders (TRD 2.5% vs nTRD 7.1%: p = 0.136) and obsessive-compulsive disorder (TRD 6.2% *vs* nTRD 8.9%: p = 0.461);
- medical comorbidities: TRD patients had higher rate of medical comorbidities (TRD 73.3% *vs* nTRD 54.4%: p = 0.002), in particular hypothyroidism (TRD 23.5 *vs* nTRD 11.8%: p = 0.018);

AD treatments before admission: as first trial, SSRI were the most prescribed (79.0%), citalopram above all (29.6%); as second and third trial, SNRI were as prescribed as SSRIs (second trial: both 32.1%; third trial: SNRI 30.8% *vs* SSRI 34.6%) and venlafaxine was the most used drug (18.5% and 19.2% at second and third trial respectively);

treatments at discharge: TRD patients were prescribed more AD drugs (TRD 1.3 ± 0.6 *vs* nTRD 1.0 ± 0.5: p = 0.003) and in particular SNRIs (TRD 32.1% *vs* nTRD 17.2%: p = 0.008), but less SSRIs (TRD 45.7% *vs* nTRD 60.4%: p = 0.003). Moreover, subjects with TRD were given more antipsychotics (TRD 51.9% *vs* nTRD 34.3%: p = 0.002) and lithium (TRD 19.8% *vs* nTRD 3.0%: p < 0.001), but less benzodiazepines (TRD 27.2% *vs* nTRD 44.4% *vs*: p = 0.009). It is noteworthy that subjects with TRD were prescribed a higher number of both psychiatric (TRD 2.4 ± 0.8 *vs* nTRD 2.1 ± 0.8: p = 0.014) and overall (TRD 3.9 ± 1.7 *vs* nTRD 3.2 ± 1.7: p = 0.008) medication compared with nTRD patients.

TABLE I. *Socio-demographic and clinical characteristics of the total sample (n = 250) and differences between TRD (n = 81) and nTRD (n = 169) patients.*

Characteristics	Total sample (n = 250)	TRD (n = 81)	nTRD (n = 169)	t/X^2	P
Age (years), mean ± SD	50.7 ± 16.1	55.3 ± 14.8	48.5 ± 16.3	-3.147	**0.002**
Gender, n (%)				1.957	0.162
– Female	126 (50.4)	46 (56.8)	80 (42.3)		
– Male	124 (49.6)	35 (43.2)	89 (57.7)		
Marital status, n (%)				5.840	0.119
– Single	89 (35.6)	24 (29.6)	65 (38.5)		
– Married/coupled	116 (46.4)	39 (48.1)	77 (45.6)		
– Divorced	28 (11.2)	14 (17.3)	14 (8.3)		
– Widower	17 (6.8)	4 (4.9)	13 (7.7)		
Education (years), mean ± SD	8.6 ± 3.3	8.7 ± 3.1	8.5 ± 3.4	0.665	0.673
Occupation, n (%)				3.556	0.469
– Working for pay	100 (40.0)	33 (40.7)	67 (39.6)		
– Housewife	21 (8.4)	7 (8.6)	14 (8.3)		
– Retired	23 (9.2)	8 (10.0)	15 (8.9)		
– Student	21 (8.4)	3 (3.7)	18 (10.7)		
– Unemployed	85 (34.0)	30 (37.0)	55 (32.5)		
Age at onset (years), mean ± SD	36.5 ± 16.8	35.7 ± 15.5	36.4 ± 17.3	0.506	0.613
Duration of illness (years), mean ± SD	14.4 ± 15.0	19.6 ± 15.8	11.9 ± 14.0	-3.898	**< 0.001**
Depressive episodes (number), mean ± SD	2.8 ± 1.6	3.2 ± 1.6	2.6 ± 1.6	-2.981	**0.003**
Hospitalizations (number), mean ± SD	2.0 ± 1.4	2.2 ± 1.2	1.9 ± 1.4	-1.088	0.123
Age at first admission (years), mean ± SD	42.6 ± 17.4	44.6 ± 14.7	41.8 ± 17.4	-6.743	**0.027**
Psychiatric family history in 1st and 2nd degree relatives, n (%)	113 (45.2)	44 (54.3)	69 (40.8)	4.024	**0.045**
Psychiatric family history for specific diseases, n (%)					
– Mood disorders	89 (35.6)	41 (50.6)	48 (28.4)	11.787	**0.001**
– Bipolar disorders	5 (2.0)	0 (0.0)	5 (3.0)	2.445	0.118
– OCD	19 (7.6)	1 (1.2)	8 (4.8)	1.952	0.162
– Suicide	19 (7.6)	12 (14.8)	7 (4.1)	18.882	**0.003**
Current episode features, n (%)					
– Psychotic	19 (7.6)	7 (8.6)	12 (7.1)	0.185	0.667
– Melancholic	16 (6.4)	10 (12.3)	6 (3.6)	7.071	**0.008**
– Anxiety	54 (19.6)	15 (18.5)	39 (23.1)	0.672	0.412
Current episode severity, n (%)				4.577	**0.032**
– Moderate	168 (67.2)	47 (58.0)	121 (71.6)		
– Severe	82 (32.8)	34 (42.0)	48 (28.4)		
Length of hospitalization (days), mean ± SD	8.1 ± 5.7	8.9 ± 4.8	7.8 ± 6.0	-1.395	0.161
Type of discharge, n (%)				1.229	0.268
– Home	184 (73.6)	56 (69.1)	128 (75.7)		
– Nursing home	66 (26.4)	25 (30.9)	41 (24.3)		
Suicide attempt leading to current hospitalization, n (%)	49 (19.6)	13 (16.0)	36 (21.0)	0.995	0.328
Current suicide attempt features, n (%)				3.453	0.632
– Nonviolent	41 (83.7)	13 (100)	28 (77.8)		
– Violent	8 (16.3)	0 (0.0)	8 (22.2)		
Lifetime suicide attempts, n (%)	68 (27.2)	21 (25.9)	47 (27.8)	0.098	0.754
Psychiatric comorbidities, n (%)	123 (49.2)	32 (39.5)	91 (53.8)	4.505	**0.034**
Specific psychiatric comorbidities, n (%)					
– Alcohol/substance use disorder	46 (18.4)	12 (14.8)	34 (20.1)	1.026	0.311
– Personality disorder	46 (18.4)	18 (22.2)	28 (16.6)	1.116	0.280
– Anxiety disorder	14 (5.6)	2 (2.5)	12 (7.1)	2.222	0.136
– Obsessive-compulsive disorder	20 (8.0)	5 (6.2)	15 (8.9)	0.544	0.461
Medical comorbidities, n (%)	153 (61.2)	61 (73.3)	92 (54.4)	10.044	**0.002**

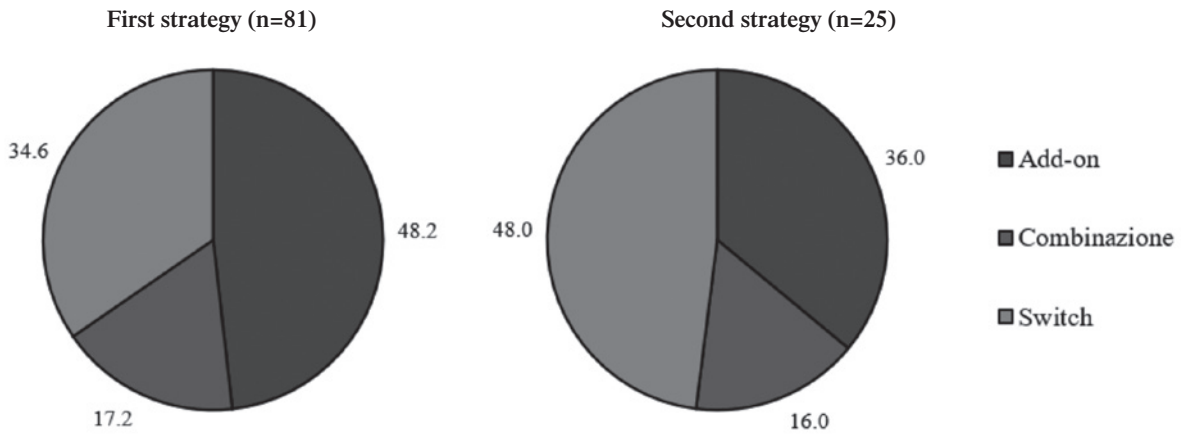

FIGURE I. *treatment strategies employed in TRD patients (n = 81) in our sample.*

Depending on the individual clinical response, a therapeutic strategy or a combination of two of the three strategies were adopted. A single strategy was preferred in most cases (69.1%), and add-on therapy was the most frequent choice (48.1%). Antipsychotics resulted in being the most frequently chosen add-on medication (68.8%), among which quetiapine (63.6%) and aripiprazole (27.3%) were the most prescribed drugs; lithium was the second most used treatment as an add-on strategy (25.0% of total). Switch to another AD was also a frequently used option (34.6%), while combination was the least preferred strategy (17.2%).
Data regarding treatment strategies employed in TRD patients is shown in Figure 1.

Discussion and conclusions

Although TRD is commonly diagnosed and treated in psychiatric wards, the population of TRD inpatients has been scarcely investigated. The purpose of the study was to deepen the knowledge of TRD features in real-world inpatients in order to provide useful information for clinicians operating in acute care hospital facilities and identify any specific characteristics of TRD in this population.
The total sample of inpatients with MDD (TRD and n-TRD) was composed in almost equal parts by females (50.4%) and males (49.6%). This is a rather unexpected finding, since MDD is widely known to be twice as frequent in females as in males [29]; moreover, inpatient settings usually include subjects with severe disease features, who are mostly women according to the literature on depressive disorders [30]. Regarding main psychiatric history features (such as age at onset and clinical course), the MDD sample conforms to recent findings in literature [31,32].
The rate of TRD (32.4%) is consistent with values reported in previous papers [33]. TRD patients presented older age compared to non-TRD, while being unemployed, lower educational level as well as being divorced/widower where not associated to treatment resistance in our sample, in contrast with findings of other studies [15,19].
As for clinical features, our sample of TRD patients showed significantly later onset of MDD, longer duration of illness and more lifetime MDEs compared to nTRD subjects, while most studies did not find such variables to be associated with treatment resistance [15,16,19]. These findings can be seen as a consequence of how TRD patients resulted significantly older than nTRD subjects in our sample, thus increasing duration of illness and number of recurrences.
A peculiar correlation emerged between TRD and family history for suicide and psychiatric disorders, mood disorders in particular. This finding does not match with results of previous studies that showed how the presence of suicide history and psychiatric disorders in first and second-degree relatives were not predictive factors for unresponsiveness to treatment [17-19]. Furthermore, a specific association between TRD and family history of bipolar disorder did not emerge in our sample. This result may suggest that patients with bipolar disorder had been successfully ruled out from the study sample, since bipolar disorder is highly characterized by specific family history and it is generally considered a cause of resistance to AD therapies [34].
Concerning specific depressive symptoms, we found a statistically significant association between melancholic symptoms and TRD, in agreement with previous data [18]. Moreover, we also found higher severity of depressive symptoms in TRD patients, that do not represent a risk factor for resistance according to the literature [15,19,20].

Data regarding suicidality is also of interest. In our sample no significant correlation emerged between TRD and suicidality, while other studies reported how current suicide attempts and history of lifetime attempts are both predictive of lack of response to therapies [13,18]. The main reason for this discrepancy may be that we did notice a high current suicide attempts rate in both subsamples (16.0 and 21.0% in TRD and n-TRD respectively), since, contrarily to previous studies, subjects enrolled were all patients in acute phase admitted to our Psychiatric Inpatient Unit. Furthermore, such unexpected finding may be related, again, to careful exclusion of patients with bipolar disorder, since patients with unipolar depression show significantly less suicidality compared to bipolar subjects [35].

There were lower comorbid psychiatric diseases in patients with TRD, although no differences were noticed in relation to specific diseases (e.g. personality disorders, alcohol/drug use disorders, anxiety disorders and obsessive-compulsive disorder). This data is not consistent with most of previous papers, which associated a higher rate of treatment resistance with anxiety disorders [16] and substance use disorders [18], while the correlation with personality disorders showed mixed results [23,24]. However, such diseases often present diagnostic issues that may have led to difficulties in carrying out optimal therapeutic strategies, with consequent misevaluation of TRD rates. Furthermore, our sample included only patients with MDD as principal diagnosis. Medical comorbidities were also related to treatment resistance in our sample, in accordance with the literature [25]. In particular, our data showed a significantly higher rate of hypothyroidism (23.5%) in TRD patients, as described in previous works [26].

Regarding pharmacological treatments at discharge, our analysis showed that TRD patients are prescribed more medication (both psychiatric and overall), most likely in relation to the higher number of medical comorbidities. A significant trend emerged in using SNRIs but not SSRIs, as the latter pertain to first-line treatments, which TRD patients often show resistance to. We registered a higher prescription of antipsychotics (in particular quetiapine and aripiprazole) and lithium in TRD, while use of benzodiazepines was significantly lower, possibly due to add-on therapy with quetiapine being very frequent in TRD subsample. In fact, add-on was the primary therapeutic strategy as it was employed in almost half of TRD patients (48.1%), whereas switch to another AD was the least used strategy. Such findings are likely influenced by the study setting (psychiatric ward with inpatients only); TRD patients were therefore in need of valid and immediately effective therapeutic options in order to obtain symptomatic remission in a very short timespan (few days of hospitalization).

Our study presents several limitations, mainly due to the retrospective design of the study. Firstly, our work did not include a follow up program after discharge, which would have allowed us to monitor long-term effectiveness of medication and therapeutic options instituted during hospitalization. Another limitation concerns the fact that therapeutic strategies are often conditioned by the clinician's experience and expertise, thus also influencing treatment options. Moreover, no treatment alternative to pharmacological treatments have been applied (e.g. sleep deprivation, light therapy, psychotherapy, somatic treatments). On the other hand, subjects enrolled for this study were real-world inpatients with MDD, contrarily to most studies conducted on outpatients.

In conclusion, the present study found that the TRD is a very frequent conditions in acute psychiatric wards, representing one-third of cases of major depressive disorder. We observed several unexpected findings, such as higher severity of symptoms, higher family history for suicide and psychiatric disorders (especially mood disorders) and lower rate of psychiatric comorbidities, that have not been described as predictive factors for TRD in literature. The lack of specific correlation between suicide and TRD is particularly noteworthy and deserving further research. Such clinical findings are strengthened by exclusion of any subtype of bipolar disorder and suggest that TRD can show peculiar characteristics depending on clinical setting. As for psychopharmacological treatments strategies in TRD patients, the lack of valid options highlights the urgent need for new compounds.

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