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Original article

Resistant or not resistant depression: that is the question

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SUMMARY

Objectives

Depression is still a leading cause of worldwide disability, and its management remains a major public health challenge. According to the most used criteria, treatment-resistant depression (TRD) is defined as an inadequate response to different classes of antidepressants administered at adequate dose and duration. However, such an assumption is not globally shared in clinical practice, and the treatment strategies for TRD are still largely empirical.
In the present study, we have sought to extend and deepen the evidence on TRD, focusing on the difficulty of its correct identification and classification, causing misdiagnosis, ineffective treatment strategies, and lack of specific guidelines for the management of TRD.

Methods

Over 12 months, 200 consecutively admitted depressed inpatients at the Mood Disorders Unit of San Raffaele Hospital in Milan were recruited. On the day of admission, according to clinical and anamnestic backgrounds, patients were classified as resistant or non-resistant, based on the staging system by Thase and Rush and the definition of TRD by Souery and colleagues. Every patient was treated with adequate pharmacological approaches and underwent a two-months follow-up after discharge. Clinical and sociodemographic variables were collected during hospitalization and follow-up.

Results

At the admission 27% of the sample displayed anamnestic drug resistance characteristics, meeting the TRD definition criteria. The resistant group differed from the responder one for older age at the admission ($p = 0.015$), more severe episodes and less psychotic features ($p < 0.001$). Analyzing the drug-specific remission rates throughout the whole sample, we observed no remission difference between drug classes (SSRI 78.20% vs SNRI 63.16% vs TCA 69.23%, $p = 0.215$). We also found no difference in remission rates between groups when treated with SSRI (non-resistant 79.03% vs resistant 75.00%, $p = 0.728$) and SNRI (non-resistant 68.18% vs resistant 56.25%, $p = 0.452$). The groups globally reached symptomatic remission in 77.88 and 59.52% of cases respectively ($p = 0.022$).

Conclusions

Studying a depressed population in mood disorders center it was possible to observe that 60% of patients categorized as treatment-resistant revealed a response to pharmacotherapies, often reaching a complete symptomatic remission using first-line treatments. This result reveals how the diagnosis of resistance could be often inaccurate and the actual pharmacoresistance prevalence much lower than what is usually shown by literature data.

Key words: depression, major depressive disorder, bipolar disorder, treatment resistant depression, TRD, antidepressant, remission, follow-up

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Introduction

Despite the incessant progress in research on mental disorders and the rapid evolution of pharmacologic therapies that occurred in the last decades, the management of patients with depression remains a major pub-

lic health challenge [1]. Depression represents a leading cause of disability worldwide and a major contributor to the overall global burden of disease remains to date [2,3].
Since the early nineties, clinical trials have shown how only half of the depressed patients respond to first-line antidepressant monotherapy, with about one-third of depressed patients will not achieve complete remission even after multiple pharmacological trials, putting the concept of Treatment-resistant depression (TRD) in the center of psychiatric research [4-6].
Because of its manifold nature, different clinical trials have used different criteria to define and describe depressed patients who show a poor response to treatment. Through the years, over 20 different TRD definitions with specific requirements (e.g., the number of trials, dosage, duration, and types of molecules) have been created and a consensus on its definition, diffusion, treatment protocols, and outcomes is lacking in the psychiatric community to date [7,8].
In clinical practice, the inability to correctly identify and classify patients with treatment-resistant depression results in misdiagnosis, ineffective treatment strategies and contributes to the lack of guidelines for the management of TRD.
Literature, often discordantly, has identified many predictors of non-response. Those characteristics are correlated with a poor outcome but do not necessarily define TRD, since these features are usually analyzed as predictors of resistance to just a single antidepressant treatment. For example, some depressive subtypes, as atypical and psychotic depression, have been usually associated with poor outcomes [9]. A number of other psychiatric variables have been identified as indicators for nonresponse to antidepressants, they may include personality disorders, anxiety comorbidities and substances or alcohol use disorder [10-12]. Medical comorbidity, delay in initiating treatment, older age and female gender are also described as major predictors of resistance [13-17]. Some of the most commonly accepted staging definitions in use today imply the failure of an antidepressant class switch as a predictor of non-response. However, such an assumption is not shared by part of the current literature [8,18-23].
As a matter of fact, the lack of precise and evidence-based guidelines for the management of treatment-resistant depression contributes to explaining why the treatment strategies for TRD are largely empirical, to date [24].
Through the great turnout of depressed patients at our tertiary referral Mood Disorders Center, we have sought to extend and deepen the evidence on this topic. We analyzed data from a 12-month period of bipolar and unipolar inpatients, focusing on subjects with histories of resistance, to explore correlations between clinical characteristics, drug resistance, different treatment strategies and remission over time.
To conduct this study, and to interpret and compare our result with the previous data available in the literature, we needed a unique operational definition of TRD. According to the most used criteria, TRD is defined by an inadequate response during the current episode to at least two trials of different classes of antidepressant at adequate doses and duration (corresponding to stage 2 of the Thase and Rush staging system for TRD, and the TRD definition proposed by Souery et al. in 1999) [8,18].

Materials and methods

As the main goal of our study was to evaluate TRD features in a realistic depressed population, we designed the present as a prospective and naturalistic study. It was conducted over a 12-month period at the Mood Disorders Unit of San Raffaele Hospital in Milan.
The inclusion criteria were > 17 years of age, fulfilling the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria for Bipolar Disorder type I or II (depressive episode) or Major Depressive Disorder, moderate or severe acute depressive episode according to *Hamilton Depression Rating Scale 21 items (HDRS-21) scores ≥ 18 at the admission.* We excluded patients with diagnosis of schizophrenia, other psychotic disorders, intellectual disability, or neurological comorbidity.
From May 2020 to April 2021, 200 consecutively admitted depressed inpatients were recruited.
During hospitalization, the presenting complaint, past medical and family history were collected in detail by a psychiatrist through daily clinical interviews.
We collected socio-demographic, clinical data, and cumulative rates of lifetime episodes of illness (mood episodes: depressive, mixed and manic). As binary variables, we assessed the presence or absence of personality disorders, active Alcohol or Substances Use Disorder and symptoms remission 2 months after discharge.
On the day of admission, according to clinical and anamnestic backgrounds, patients were assigned to a group:

- non-resistant (n = 146): responders in past episodes (if any), with no characteristics of resistance in the current episode;
- resistant (n = 54): subjects with inadequate response during the current episode to at least two trials of different classes of antidepressant at adequate doses and duration.

Personality disorders were assessed through SCID-5 for Personality Disorders (SCID-5-PD). The severity of depressive symptoms and remission over time were weekly assessed through HDRS-21.

According to clinical judgments all patients were treated with adequate pharmacological approaches, following during hospitalization an individualized rehabilitation program.
Every patient underwent follow-up visits up to two months after discharge.
The study, approved by the Ethical Committee of the Hospital, was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical analyses

To investigate group differences in clinical and socio-demographic variables, compare treatments during hospitalization and drug-specific remission rates over time, we performed a Mann-Whitney U test and Chi-Squared test for continuous and categorical variables, respectively. When the value in any of the cells of a contingency table was below 5, we used Fisher's exact test. Normality was checked by the Shapiro-Wilk normality test.
All statistical analyzes were performed using JASP (Version 0.14.1) Computer software; charts and tables were generated by JASP or Microsoft EXCEL [25,26].

Results

Over 12 months, a total of 200 unipolar and bipolar depressed inpatients were included in the present study (mean age 59.76 ± 12.10 years; age range 24-82 years; gender (female/male), 134/66; unipolar/bipolar depression, 73/127).
On the day of admission, we stratified the sample for resistance to treatment: 27% of the sample displayed anamnestic drug resistance characteristics, meeting the criteria of TRD definition: inadequate response during the current episode to at least two trials of different classes of antidepressant at adequate doses and duration.
Clinical and socio-demographic data of the two groups are displayed and compared in Table I. The only socio-demographic variable that differs (by Mann-Whitney U test) between groups was the age of admission: the non-resistant group was younger than the resistant one (non-resistant 58.58 ± 11.73 *vs* resistant 62.98 ± 12.61 years; p = 0.015).
Evaluating the severity and presence of psychotic features of the depressive episode we found by chi-square test a statistically significant difference between groups. *Non-resistant group*: moderate 110 subjects (75.34%), severe 19 subjects (13.01%), severe with psychotic features 17 subjects (11.64%) *vs resistant group*: moderate 33 subjects (61.11%), severe 19 subjects (35.19%), severe with psychotic features 2 subjects (3.70%), p < 0.001.
The two groups differed by chi-squared test (p = 0.003) in the treatment received during hospitalization: the *non-resistant group* was treated mainly with SSRI (86 patients, 64.18%), 25 patients (18.66%) with SNRI, 23 patients (17.16%) with TCA; in the *resistant group* 21 patients (40.39%) where treated with SSRI, 22 patients (42.31%) with SNRI, 9 patients (17.31%) with TCA.
The two groups of patients achieved and maintained by chi-squared test a different remission rate at two months after the discharge: non-resistant 88 patients (77.88%) vs resistant 25 patients (59.52%), p = 0.022.
Analyzing the drug-specific remission rates throughout the sample, we found no difference between drug classes (SSRI 78.20% *vs* SNRI 63.16% *vs* TCA 69.23%, p = 0.215 by chi-squared test). We also found no difference in drug-specific remission rates between groups when treated with SSRI (non-resistant 49 remitters, 79.03% *vs* resistant 12 remitters, 75.00%, p = 0.728 by chi-squared test) and SNRI (non-resistant 15 remitters, 68.18% *vs* resistant

TABLE I. *Clinical and socio-demographic data. * Chi-Squared test ** Mann-Whitney U test.*

	Non-resistant (n = 146)	Resistant (n = 54)	P-value
Diagnosis (DMR/BD)	89/57	38/16	0.220*
Age, y	58.58 ± 11.73	62.98 ± 12.61	0.015**
Episodes of illness, n	3.64 ± 2.04	4.02 ± 1.92	0.130**
Personality disorders	32.19%	18.52%	0.057*
Alcohol abuse	6.85%	3.70%	0.406*
Substance abuse	4.80%	3.70%	0.741*
Episode type:			< 0.001*
moderate	110 (75.34%)	33 (61.11%)	
severe	19 (13.01%)	19 (35.19%)	
with psychotic features	17 (11.64%)	2 (3.70%)	

9 remitters, 56.25%, p = 0.452 by chi-squared test). Statistically significant differences in remission rates between groups were achieved by the patients treated with TCA (non-resistant 15 remitters, 83.33% *vs* resistant 3 remitters, 37.50%, p = 0.027 by Fisher's exact test).

Discussion

On the day of admission, 27% of our sample displayed pharmacoresistant characteristics, a percentage is in line with the most reliable literature on the topic that reported about 25-30% [4-6].

Stratifying the sample for anamnestic resistance to treatment, we identified two groups of patients: *non-resistant* and *resistant.* The groups appeared similar in diagnosis distribution, gender, lifetime episodes of illness, alcohol and substance abuse, presence of personality disorders as if these clinical and socio-demographic characteristics would be unrelated to the definition of TRD. The literature about this topic is mostly controversial, it lists several characteristics as correlates for a worse outcome following a depressive episode, but not necessarily defining TRD [9-17].

Conversely, we found a correlation between the age of the subjects and resistance to treatments. This is in accordance with great literature which highlights older age as one of the major risk factors for the development of TRD (because of poor medical health, brain atrophy and cognitive impairment, loneliness, retirement, financial problems, losses, poly-therapies) [14-17].

We also observed a relationship between the severity of a depressive episode and the presence of pharmacoresistance: greater severity, causing functional impairment, was related to decreased responsiveness to treatment [27].

Although many studies consider psychotic features as a specific risk factor for poor response to treatment [28], in our sample we found that the few patients who displayed psychotic symptoms during the depressive episode belonged mostly to the *non-resistant* group; as if psychotic manifestations could be a sign of *endogenous depression*, which, unlike *reactive depression*, it is usually unrelated to stressful environmental factors and personality disorders, therefore more responsive to pharmacotherapy alone.

Non-resistant and *resistant groups* during the hospitalization received by clinical judgment different treatment strategies (*the non-resistant group* was mostly treated with first-line pharmacotherapies: choice of SSRI for 64.18% of *non-resistant vs* 40.39% of *resistant*), reaching remission of symptoms in 77.88 and 59.52% of cases, respectively. Notable was the finding that no outcome differences emerged between different drug classes, studying the whole sample. This finding is concordant with a previous report of Souery et al. [8], that showed how switching antidepressant classes does not improve remission rate in TRD.

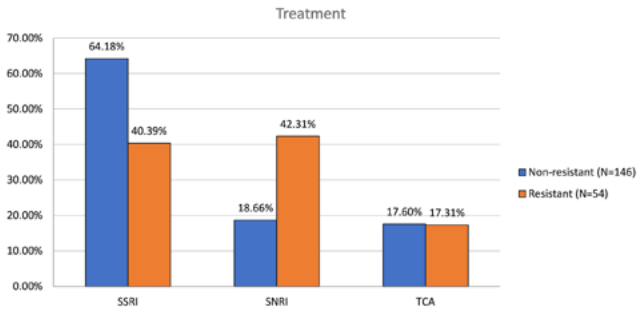

FIGURE 1. *Treatment received during hospitalization, p = 0.003.*

We tried to go deeper into this topic, stratifying the sample for resistance to treatment, we analyzed the drug-specific remission rates between groups: no differences in outcome at 2 months after discharge was found between resistant and non-resistant patients when treated with SSRI or SNRI. Conversely, statistically significant differences in remission rates between groups were achieved by the patients treated with TCA: *non-resistant* patients reached a much higher remission rate than *resistant* ones, more than 80% *versus* less than 40%.

The results suggest that TCAs are chosen by clinical judgment in the most complex and difficult-to-treat cases, moreover extensive literature shows how atypical depression and specific symptoms as psychomotor agitation, and anxiety may show a poor response to TCAs [9,29,30]. Regarding the *non-resistant* group, if com-

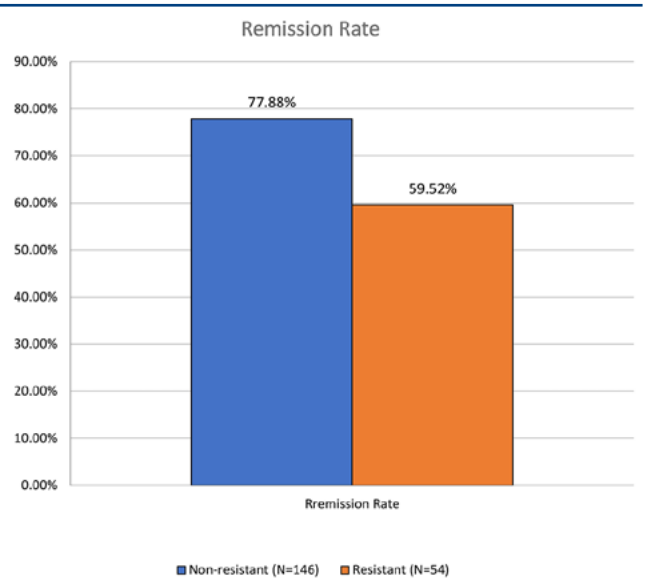

FIGURE 2. *Remission rate between groups at the end of the 2-months follow-up, p = 0.022.*

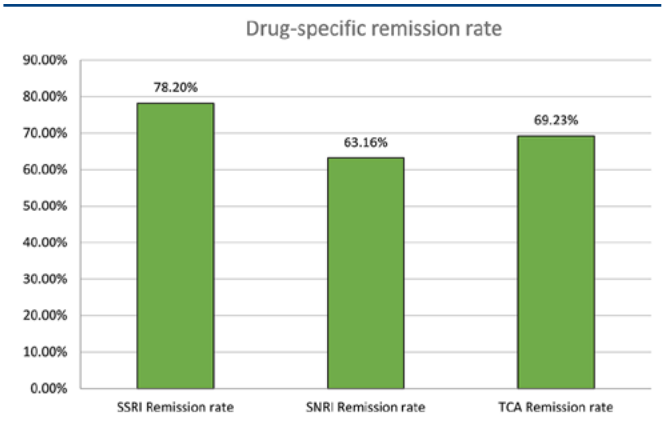

FIGURE 3. *Drug-specific remission rate in the whole sample, p = 0.215.*

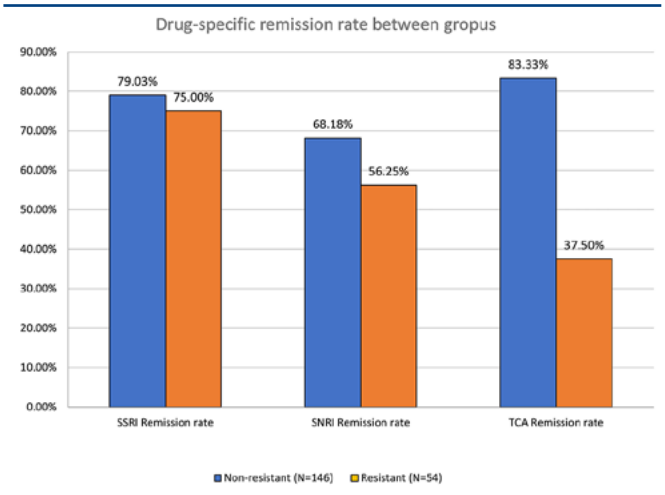

FIGURE 4. *Drug-specific remission rate between groups, SSRI p = 0.728; SNRI p = 0.452; TCA p = 0.027.*

pared to other drug classes, TCAs reached the highest remission rate, but without statistical significance.
Our finding could have many practical consequences in the clinical management of depressed patients, both for resistant and non-resistant, inasmuch it shows the effectiveness of different pharmacotherapies lines in relation to pharmacoresistance characteristics. Notably, first-line treatments appeared to be equally effective in both groups, ensuring globally the higher remission rate.
As a matter of fact, the management of TRD in our unit already considers, whenever possible, the use of first-line treatments: in this study, we treated about 40% of resistant patients with SSRIs obtaining the same or better remission rate than what described in the literature [4-6,24].
Finally, it was very interesting to observe how almost 60% of patients who displayed anamnestic drug resistance characteristics on the day of admission obtained clinical remission throughout the study. It revealed that the diagnosis of resistance could be often inaccurate, since the actual percentage of drug resistance in that group was 40.48% indeed, much lower than what is usually shown by literature data [4-6].

Conclusions

We studied a depressed population with a diagnosis of unipolar and bipolar disorder in a mood disorder and we observed that about 60% of patients categorized as treatment-resistant revealed a response to pharmacotherapies, often reaching a complete symptomatic remission using first-line antidepressant treatments.
Analyzing the drug-specific remission rates we found no difference between groups when treated with SSRI and SNRI, and a higher remission rate in the responder group just when treated with TCA.
It is probably limiting to consider TRD as a unique subtype of depression, and therefore the use of staging models could be useful to better characterize and improve the homogeneity of future studies. Anyway, most accepted staging definitions in use today appear to be misleading in the clinical practice because they do not appear to be predictive of response and may guide clinicians towards more complex therapeutic lines without an actual outcome improvement.

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None.

Conflict of interest statement

The Authors declare no conflict of interest.

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Authors' contributions

All the Authors contributed to the design, the draft and the analysis of the work. All authors revised the work and and approved the final manuscript.

Ethical consideration

This study was approved by the Institutional Ethics Committee (IRCCS San Raffaele Hospital, Milan, Italy) (protocol number 10-06-SO).
The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each participant/patient for study participation and data publication.

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