Incidence of treatment-resistant depression during the first mood depressive episode
Incidence de la dépression résistante lors du premier épisode dépressif

Maroua Said[1], Rania Hosni[2], Hend Jemli[2], Yosra Zgueb[2], Uta Ouali[2], Haifa Zalila[3], Fethi Nacef[2], Rabaa Jomli[2],

1. *Public Mental Health Establishment in Marne (France).*
2. *Psychiatry Department A, Razi hospital, Tunis, Tunisia*
3. *Outpatient Psychiatry Department, Razi Hospital, Tunisia*

Abstract

Background: In spite of several approaches and therapeutic measures, treatment-resistant depression (TRD) continues to inflict serious, individual and collective consequences. Therefore, there is a persistent need to scrutinize the concept of TRD in order to adapt the therapeutic strategies.
Aim : To estimate the incidence of TRD in patients with a first major depressive episode (MDD), and study factors associated with resistance.
Methods: A descriptive prospective longitudinal study of outpatients with a first MDD, was conducted. Patients with a history of subthreshold hypomania were excluded. Eligible patients were put on a selective serotonin reuptake inhibitor (SSRI), either fluoxetine or sertraline. Participants were followed regularly until they had a therapeutic response or they met the criteria for TRD.
Results: The study involved 82 adults. The incidence of treatment-resistant depression was 19.4% CI95%=[5.5-33.3]. Among the sociodemographic and clinical factors, family history of psychosis (p=0.038) and chronic respiratory comorbidities (p=0.016) were associated with TRD. The small size of the sample is a potential limitation of this study. Besides, the use of only two SSRIs could influence the results.
Conclusion: In this study, the incidence of TRD was at the lower limit of the rates reported in clinical studies. Clinical factors associated with TRD suggest the relevance of genotype analysis to identify patients with TRD. Furthermore, our results highlight the importance of heeding comorbidities to optimize care. Larger multicenter studies are sneeded to generalize

Key words: resistant depression, incidence, fluoxetin, sertralin

Résumé

Introduction : La dépression représente un problème majeur de santé publique. Le préjudice de cette maladie, est dû pour une part importante à la résistance, qui peut aboutir à la chronicité.
Objectif : Estimer l'incidence de la dépression résistante au cours d'un premier épisode dépressif majeur et rechercher les facteurs sociodémographiques et cliniques associés à cette résistance.
Méthodes : Une étude descriptive longitudinale et prospective a été menée, auprès des consultants à l'hôpital Razi, pour un premier épisode dépressif majeur. Les patients inclus dans l'étude ont été mis sous traitement antidépresseur, à base de fluoxétine ou sertraline. La première phase de traitement a consisté de suivre la réponse au premier antidépresseur avec un contrôle tous les quinze jours et une augmentation de la dose jusqu'à la dose maximale. En l'absence de réponse au premier antidépresseur, un swich pour le deuxième antidépresseur est fait avec contrôle tous les quinze jours et augmentation de la dose jusqu'à la dose maximale. Les participants ont été suivis régulièrement jusqu'à l'obtention d'une réponse thérapeutique ou bien la réunion des critères d'une dépression résistante.
Résultats : Notre étude a intéressé 82 patients, ayant un âge moyen de 44,5±11,1 ans. Des antécédents familiaux de trouble dépressif ont été notés chez 17,3% des patients, de trouble bipolaire chez 11,1%, de trouble psychotique chez 13,6%, et de trouble anxieux chez 14,9%, alors que 14,7% avaient un trouble de la personnalité. Chez notre population, le taux de réponse au premier antidépresseur était de 47,2%. Le taux de réponse au deuxième antidépresseur était de 57,1%. L'incidence de la dépression résistante, chez notre population, était de 19,4%. Une association statistiquement significative entre la dépression résistante et la présence d'antécédents familiaux de psychose d'une part, et d'autre part avec les comorbidités respiratoires chroniques a été retrouvée.
Conclusion: L'incidence de la dépression résistante dans ce travail se situe dans la limite inférieure des chiffres de prévalence de la résistance rapportés dans la littérature. Les facteurs cliniques prédictifs de résistance contribuent probablement à identifier ces patients. Dans le futur, l'analyse génotypique permettra probablement une évaluation plus sensible et plus précoce de la réponse thérapeutique.

Mots clés : dépression résistante, incidence, fluoxetine, sertraline

Correspondance
Rabaa Jomli
Psychiatry Department A, Razi hospital, Tunis, Tunisia
Email : jomli.rabaa@gmail.com

INTRODUCTION

Depression is the most prevalent mental illness that affects more than 264 million individuals worldwide (1,2). According to the World Health Organization (1), the long-lasting evolution of this illness makes it a serious health condition. In this common case, its negative impact becomes significant on all aspects of the individual's functioning (1,3). Human and economic costs of this condition are enormous, especially, in the case of treatment-resistant depression (TRD) (4-6) . As shown in statistics, TRD annual direct costs were 40% higher than those for non TRD (7). By way of example, the mean annual total societal cost of TRD in the United Kingdom was estimated at £22 124 (4,5). In addition to its impact on morbidity, TRD was associated with a higher risk of suicidal and non-suicidal mortality (8,9). In fact, resistance multiplies the risk of suicide attempt by 2, let alone the significant proportion of euthanasia requests motivated by TRD (8-12) . Even mortality after a myocardial infarction was twofold higher in patients with TRD than those treated for Major Depressive Disorder (MDD) (13). These data highlight the persistent need for optimizing therapeutic measures in order to alleviate this burden. However, reliable assessment of TRD is a key step to improve the quality of clinical care and research (8,14). Indeed, the WHO pointed out the inaccurate assessment as a barrier to effective care for depressive individuals (1).

Since 1970, there has been an ongoing debate about finding an adequate approach and criteria to identify resistant patients (14,15). Despite the burgeoning definitions and staging systems, there is not any consensual definition of TRD (16,17). Nonetheless, the most commonly

used definition is based on the failure of two successive trials of antidepressant at a sufficient dose and duration (17,18). This broad diversity could explain the divergence of methods and hence TRD prevalence and its risk factors (19-22). Not surprisingly, a recent systematic review has concluded that only 17% of intervention studies considered the most common definition of TRD (17). Nevertheless, all definitions are based on two parameters: treatment adequacy and response rating (23). But the debates stressed prominently the overlook of two fundamental factors in studies rating TRD, namely, the diagnosis of depression and its treatment history (15). In fact, not to mention the blurring confusion between unipolar and bipolar depression, several conditions could overlap with MDD for which antidepressants aren't effective (15-24). Besides, treatments weren't as effective in wide samples of non-responders as in clinical trials (15-24). Moreover, it has been shown that the assessment of previous trials is often unreliable (25). Consequently, it seems uncertain to establish the number of previous failed adequate trials (23,26). Thus, only 33% of a sample of patients with a chronic depression were at least put on one adequate medication trial (27).

This leads to inconclusive TRD rating and ergo compromises its treatment relevance and consequent efficacy (23,28,29).

Moreover, Malhi and al concluded that the problem with TRD extends from the outset (15). Especially that TRD risk factors has often been linked to previous depressive episodes' outcome and illness duration (30-32). In fact, it was established that the loss of an antidepressant efficacy may adversely influence the response to a subsequent trial (25). Even the caregiver burden, dealing with patients deemed resistant, may affect the outcome (33,34).

This emphasizes the determining effect of initial therapeutic care and outcome in diagnosing "pure" TRD in order to define its enigmatic features. Hence, the challenge is to identify individuals with "pure" TRD to improve our knowledge about this endophenotype so as to help along with the optimization of its treatment options. These data suggest the reliability of assessing prospectively TRD during the first MDD episode. While TRD prevalence has been investigated, no prospective study, to our knowledge, has been carried out to estimate the incidence of TRD, and to explore its risk factors during a first mood depressive episode.

METHODS

A descriptive prospective longitudinal study was conducted. Patients were recruited between September 2018 and January 2020 in the outpatient psychiatric department of the Razi hospital in Tunis (Tunisia).

Patients

The inclusion criteria were outpatients with the diagnosis of first MDD according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders, in its revised text (DSM- IV), aged between 18 and 65, and who granted their informed consent after attending to a complete description of the study.

Patients who were prescribed beforehand an antidepressant treatment or who were women in peripartum period or had lifetime histories of MDD, bipolar disorder, psychotic disorder or mental retardation, were not included. Exclusion criteria were a Hypomania Checklist 32 (HCL 32) score predictive of a previous subthreshold hypomania, indication of hospitalization or of prescribing a medication with a mood stabilizing effect and treatment discontinuation by patients because of unsustainable side effects.

Assessment measures

Hypomanic episodes screening was first performed using the Hypomania Checklist 32 (35-37).

During the study, severity of depressive symptoms was assessed with the Hamilton Depression Rating Scale with its 17 items (HDRS 17) (38). Severity of symptoms was measured at baseline and bimonthly until treatment response achievement or meeting criteria of TRD. Treatment response was defined as HDRS 17 total score reduction of at least 50%. In this study, we considered the most commonly used definition of TRD as the failure to respond to two antidepressants each prescribed at sufficient doses and during a sufficient period (17,18).

Sociodemographic and clinical data were gathered from patients through a semi-structured interview.

Study design

After initial assessments, eligible patients were put on a selective serotonin reuptake inhibitor (SSRI). Antidepressants used in this study were SSRIs that are available in Tunisian hospital drugs list: fluoxetine and sertraline. The choice of antidepressant was made by the caregiver based on the basic principles of prescribing. At baseline, the minimum effective doses of SSRIs were introduced (IE fluoxetine 20 mg and sertraline 50mg). If adjunctive sedative or anxiolytic treatment had been needed, patients would have gotten prescribed hydroxyzine or lorazepam. For each patient, a bimonthly follow up was conducted. Four weeks later, if HDRS 17 reduction had been < 50%, dose optimization would have been performed. After 6 weeks of treatment, unless there is a response, patients switched from the ongoing SSRI into the second one. During the second phase, the same rhythm of follow up was conducted. Dose optimization had the same indication 4 weeks after the switch. In this study, all assessments were carried out by the same investigator.

Statistics

All analyses were performed using the 21st version of SPSS. Descriptive statistics of study included, among others, the calculation of the cumulative incidence rate of response and resistance with the 95% confidence interval (95% CI) of each of these rates. According to comparative statistics between responders and resistants, as the distribution of continuous variables in our study deviated significantly from the normal distribution for at least one of the two groups, the comparison of two means was performed by a non-parametric test: the Mann-Whitney U test. The distribution of continuous variables in each of the groups (responders vs. resistants) was compared to a normal distribution using the Shapiro-Wilk test. To compare percentages, the Pearson Chi-square test was used. In case of non-validity of this test, we used the exact bilateral Fischer test. In this case, and if necessary, several categories were collected to have 2 * 2 cross-tables allowing the use of the Fischer bilateral exact test. The significance threshold $p<0.05$ was considered for all statistical tests.

Ethical considerations

All the study steps were conducted in accordance with the Helsinki Declaration as revised in 1989.

RESULTS

Descriptive results

Our study involved 82 out-patients. The main Socio-demographic and clinical features of our population are recapped in Tables 1 and 2.

Table 1. Socio-demographic characteristics of the population

n	82
Age, years (m ±SD)	44.5±11.1
Gender, % females	68.3
Socio-economic level, %	
Low	38.0
Middle	58.2
High	3.8
Educational attainment, %	
Illiterate	12.3
Primary	29.6
Secondary	35.8
University	22.2
Work status, %	
Unemployed	35.8
Worker	33.3
Official	22.2
Other statue	8.7
Marital status, %	
Single	12.3
Married	63.0
Divorced	14.8
Widowed	9.9

SD : Standard Deviation ; m : mean

Table 2. Clinical characteristics of the population

n	82
Family history	
Depressive disorders, %	17.3
Bipolar disorders, %	11.1
Anxiety disorders, %	14.9
Psychotic disorders, %	13.6
Suicide attempt, %	14.9
Childhood abuse, %	17.5
Suicide attempt, %	22.8
Comorbid psychiatric illness, Axis I, %	8.5
Tobacco addiction, %	35.8
Alcohol dependence, %	2.5
Dependence on other substances, %	4.9
Personality disorders, %	
Paranoid	1.3
Narcissistic	1.3
Histrionic	8.0
Borderline	4.0
Somatic comorbidity, %	76.6
HCL 32 score (m ±SD)	11.8±17.6
HDRS baseline score (m ±SD)	22.9±5.6
Severity of depressive symptoms, %	
Mild	2.4
Moderate	24.4
Severe	73.1

SD : Standard Deviation ; HCL 32 : Hypomania Check List 32 ; HDRS : Hamilton Depression Rating Scale ; m : moyenne

Among 82 participants that fulfilled the inclusion criteria, nine were excluded because of positive HCL 32 score. Seventy-three patients undertook the first phase of the protocol, 3 of whom were excluded after antidepressant discontinuation because of intolerance or necessary prescription of medications with mood stabilizing effects. During this first phase, 34 patients were lost to follow-up. At the end of this phase, 17 participants responded to antidepressant treatment, while the switch to the second antidepressant was undertaken in the 19 others. Among these 19 non-responders to the first antidepressant, five were lost to follow-up and eight showed at least a 50% improvement under the second treatment. Thus, six participants did not respond to the second trial of antidepressant. In summary, 12 patients were excluded and 39 others dropped out. Among the 82 patients initially included, 31 adhered entirely to the study: 17 responded to the first antidepressant, 8 responded to the second and 6 did not respond to any of the two trials. Figure 1 illustrates all phases' findings.

After eliminating patients who dropped out and who were excluded, the response rate to the first antidepressant was 47.2% (95% CI [30.9-63.5]) and the response rate to the second one was 57.1% (95% CI [31.2-83.0]). According to the maximum bias hypothesis, the response rate to the first trial was 23.3% (95% CI [13.6-33.0]) and the response rate to the second was 42.1% (95% [19.9%-64.3%]). In this study, TRD incidence was 19.4% (95% CI [5.5-33.3%]).

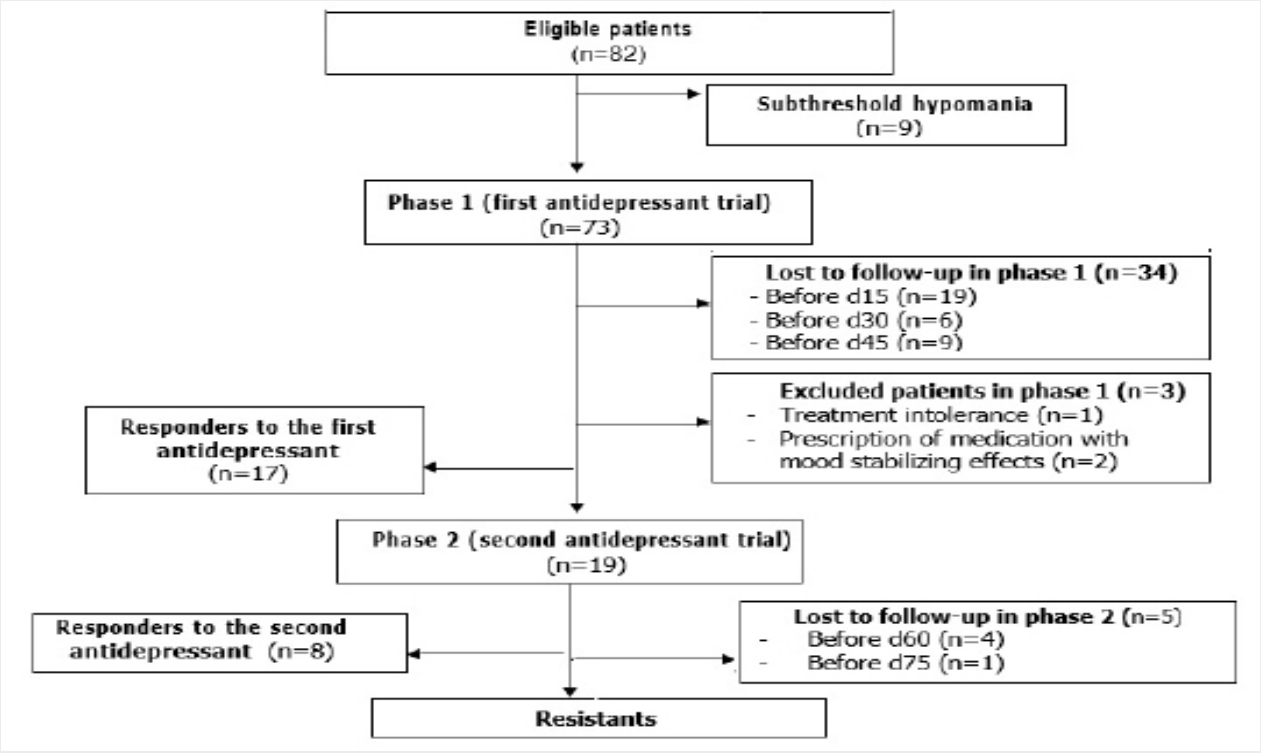

Figure 1. Participants through the study phases

Correlation analyses

Considering socio-demographic variables, responders and resistants did not significantly diverge. The two groups were also comparable in terms of family histories of bipolar disorder, depression and suicide attempt. Whereas, resistance was positively correlated to family history of psychosis (p=0.038).

Comparison of trauma, suicide attempt histories, and psychiatric addictive and non-addictive comorbidities did not reveal any statistically significant difference between the two groups. Regarding somatic comorbidities, only chronic respiratory conditions were significantly more frequent among resistants (p=0.016). Correlation analyses didn't find any statistically meaningful difference, neither in initial scores of HDRS nor in HCL 32 scores between responders and resistants. Tables 3 and 4 summarize all the results of comparative analyses.

Table 3. Assessment of correlations between resistance and sociodemographic factors

	Resistants	Responders	Statistical test	p
n	6	25		
Age, years (m ±SD)	47.3	42.0	Mann-Whitney U	0.158
Gender, % females	50.0	68.0	Fischer exact test	0.638
Socio-economic level, %			Fischer exact test	1.000
Low	33.3	28.0		
Middle or High	66.7	72.0		
Educational attainment, %			Fischer exact test	0.653
Illiterate or Primary	50.0	36.0		
Secondary or University	50.0	64.0		
Work status, %			Fischer exact test	1.000
Unemployed	33.3	44.0		
Worker	66.7	56.0		
Marital status, %			Fischer exact test	0.358
Single	28.0	50.0		
Married, Divorced or Widowed	72.0	50.0		

m : mean

Table 4. Assessment of correlations between resistance and clinical factors

	Resistants	Responders	Statistical test	p
n	6	25		
Family history				
Depressive disorders, %	0.0	12.0	Fischer exact test	1.000
Bipolar disorders, %	0.0	4.0	Fischer exact test	1.000
Anxiety disorders, %	16.7	4.0	Fischer exact test	0.355
Psychotic disorders, %	50.0	8.0	Fischer exact test	0.038
Suicide attempt, %	0.0	8.0	Fischer exact test	0.774
Childhood abuse, %	40.0	9.5	Fischer exact test	0.155
Suicide attempt, %	50.0	20.0	Fischer exact test	0.161
Comorbid psychiatric illness				
axis I %	0.0	4.0	Fischer exact test	1.000
Tobacco addiction, %	33.3	28.0	Fischer exact test	1.000
Alcohol dependence, %	0.0	0.0	-	-
Dependence on other substances, %	0.0	3.2	Fischer exact test	1.000
Personality disorder, %	16.7	21.7	Fischer exact test	1.000
Somatic comorbidity, %	83.3	84.0	Fischer exact test	1.000
Chronic respiratory disease, %	50.0	4.0	Fischer exact test	0.016
HCL 32 score (m)	11.5	11.1	Mann-Whitney U	0.268
HDRS baseline score (m)	26.2	22.0	Mann-Whitney U	0.929

HCL 32 : Hypomania Check List 32 ; HDRS : Hamilton Depression Rating Scale ; m : mean

DISCUSSION

This study is the first to estimate the incidence of TRD during a first MDD in a Tunisian cohort. We aimed also to explore the "pure" predictors of TRD. We first explored the cohort sociodemographic and clinical features. The sociodemographic profile of our population was similar

to other larger samples in the literature (39) except the socio- economic levels, which were more frequently low and middle in our sample compared with the STAR*D's population40. Concerning clinical data, severe intensity of symptoms was more common in our study (73.1%) than in the European multicenter study (59.8%) (30).

Then, we calculated response rates and resistance's incidence. The response rate to the first trial of antidepressant was 47.2% (95% CI [30.9-63.5]). This result is in concordance with previous larger studies that used several classes of antidepressants prescribed at effective dose during at least 6 weeks (19,41,42).

The response rate to the second trial was 57.1% (95% CI [31.2-83.0]). As shown in the meta-analysis of Rhué and al, in case of failure to respond to a first SSRI, the response rate to the second one ranged between 46 and 58% (43). This rate was seen higher when the switch was after an intolerance to treatment (43-45). A lower rate, 48.5%, was recorded after a switch from fluoxetine to mianserine (46). This result highlights, as the majority of studies, the disadvantages of switching to other classes of antidepressants47. In STARD*D, response rates to the second trial ranged around the half of our rate, regardless of the above two conditions. This difference could be due to the prominent proportion of patients with recurrent (72%) and chronic (27%) depressive disorder (41,48). The response rate to a second trial was also lower (42%) in a sample of inpatients, in spite of the use of the same molecules (49). In fact, inpatient status was shown as a predictor of treatment resistant depression (30).

Among our patients, 19.4% (95% CI [5.5-33.3%]) met criteria for TRD while 35% of patients in STAR*D met these criteria48. The non-exclusion of patients with probable bipolar depression in addition to the presence of comorbid psychiatric disorders in two thirds of the sample in STAR*D could explain this difference. Our rate was also lower than the rates of the European multicenter study (50.7% and 63.6%) (9,30). This could be explained by the retrospective assessment based on the Souery staging model. Regarding primary care, the prevalence of TRD (21.7%) in Canada was very close to our rate in spite of the use of criteria requiring switching to a different class of antidepressants (22). Assessments of TRD prevalence based on insurance databases ranged between 6.6 in the USA and 20.94% in Taiwan (28,50,51). In these large studies, the diagnosis of TRD was based on treatment switch or discontinuation, regardless of the underlying reason with doubtful dose adequacy.

Association between resistance and several social, demographic and clinical factors have been examined. These analyses didn't reveal any link between several sociodemographic factors and resistance. Fife and al, whose sample included elderly, have found an increase in incidence of TRD with age and in females (50). Metabolic slowing, comorbidity and polypharmacy increase with age which could lead to resistance as well as to intolerance to treatment (52). Interestingly, in the same study, TRD incidence decreased in females aged ≥60 (50). Before menopause, several studies have shown better response to SSRI and poorer response to tricyclics in females compared with males (53,54). These findings shed important light on the role of hormonal status of women in response to treatment, beside the influence of the psychosocial context. Likewise, in literature, patients with poor response to treatment were more likely to be unemployed, with low socioeconomic status and/or low educational attainment, single or divorced (22). Regarding clinical factors, we didn't find a link between resistance and family history of depression, as well as in STAR*D and in the European multicenter study (9,55) . However, heredity and genetic determinants of response to SSRIs were documented (56). In this study, we didn't note family history of bipolar disorder among resistants, but we found interestingly an association between resistance and family history of psychotic disorders (p=0.038). As bipolar diathesis was identified as a prominent explication of TRD (57), this finding is consistent with the increasing evidence of a partial common genetic etiology of schizophrenia and bipolar disorder (58). Furthermore, it was shown that these disorders share the same epigenetic alterations which mirrors the evidence of the common environmental risk factors (59) . In addition, Green and al pointed out a polymorphism CACNA1C that could predispose to bipolar disorder, recurrent depressive disorder as well as to schizophrenia (60). Rhimer and al assessed that about the third of patients with TRD have a subthreshold bipolar disorder (57). Likewise, 20.5% of diagnostic conversions from MDD into bipolar disorder, after 9.27±8.64 years, were in TRD cases (61). In this study, we didn't observe a significant association between neither family nor personal

history of suicide attempt and TRD in accordance with the European multicentre study (TDR I) (9,30).

Whereas, suicidal risk was a replicated predictor of TRD in TRD I and TRD III studies (9,30). On the other hand, family suicidal behaviours figured among the underlying factors of hypomania in Bipolact survey (62). Hence, beside the small sample, the exhaustive exclusion of patients with subthreshold hypomania in our study could explain these results.

Regarding severity of symptoms, there was no significant difference between the mean HDRS scores of resistants and responders. Symptom severity was a replicated predictor in the European multicenter studies30. Baseline symptoms' severity was also linked to poor response in STAR*D (63). This predictive value was inverted in chronic depression (64). But it also depended on the psychometric scale (64). In our sample, we didn't find a link between psychiatric comorbidity and resistance. In literature, comorbid anxiety disorders were frequently associated to poor response and TRD (30,42,65).

Concerning psychoactive substances, alcohol consumption, even non excessive as well as other psychoactive substance abuse were associated with poor prognosis (9,30,66). On the axis II, personality disorders were weakly associated with resistance in the European multicenter study TRD I (9,30). A systematic review and meta-analysis refuted the negative effect of personality disorders on pharmacotherapy response in MDD (67).

In our study, somatic comorbidities were equally distributed between resistants and responders. This finding agrees with the results of the European multicenter studies contrary to others like the STAR*D (22,30,68). According to Fava and Davidson, somatic comorbidities don't have all the same impact on the outcome (19). This impact was also attributed to medication intolerance (11). Consequently, this negative effect was weaker in samples treated with SSRIs (69,70).

In our sample, chronic respiratory conditions were significantly more frequent in resistant patients. In this context, chronic obstructive pulmonary disease (COPD) was associated with TRD in the Canadian study (22). These findings could be due to the longer treatment effectiveness delay (estimated at 12 weeks) in these conditions (71,72). Indeed, cytokines lead to the degradation of tryptophan while the interleukin 1 ß and the TNF ¤ upregulate the serotonin transporter SERT which could influence SSRI's efficacy (73). In addition, both chronic respiratory diseases and depression affect energy, sleep and appetite (74).

Hence, stabilization of chronic respiratory conditions was linked to the improvement of depressive symptoms (74,75). Conversely, a positive effect of sertraline on dyspnea in patients with COPD has been suggested (76).

Limitations

To carry out this study, we have been confronted with some choices and methodological difficulties. The main limitation is the relatively small size of the sample which could explain some negative results. In fact, our study involved only outpatients of Razi Hospital. This public center provides the inhabitants of northern Tunisia with secondary and tertiary care. Thus, involving patients with a first MDD and before the prescription of any antidepressant wasn't so common to have sufficient statistical power. In addition, this could inflict a selection bias as this hospital is attractive to patients with severe symptoms or with low income. We didn't also randomise the order of antidepressants, which could influence the results. To ensure the optimal course of care, we entrusted the choice of antidepressant to the attending psychiatrist. Especially that it has been shown shown that Fluoxetine and Sertraline have similar efficacy (77). Therefore, we didn't randomise the order of antidepressants, which could influence the results. As a common problem of prospective studies, we registered a significant rate of lost to follow-up. The choice of antidepressant was restricted to the two-second generation molecules available at the hospital, especially that Sertraline and Fluoxetine belong to the same class of SSRI. However, apart from the serotonin transporter inhibition, Fluoxetine and Sertraline do not have the same mechanisms of action (78).

CONCLUSION

In conclusion, among 82 outpatients with a first episode of MDD, and after the exclusion of 9 participants because of positive screening of subthreshold hypomania, 19.4% met criteria of TRD after the failure to respond to 2 trials of antidepressants. Patients with TRD had significantly more family history of psychosis and more chronic respiratory diseases. These results shed light on the overlapping familial patterns in schizophrenia, bipolar disorder as well as in TRD. Hence, even after an exhaustive exclusion of bipolarity, bipolar diathesis appears to be an underlying

cause of TRD. In literature, according to the current diagnostic criteria and tools, this diathesis was explicitly noted in about the third of cases of TRD. However, even unipolar depression could resist to treatment like in patients with chronic respiratory disease. This highlights the importance of taking into account the specific impact of comorbidities in order to optimize care.

This study suggests two clinical predictive factors of TRD, especially independently of the impact of previous episodes. Larger studies could allow the generalization of these results. That also implies the probable contribution of genotype analyses in the future to lead to an earlier diagnosis.

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