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# Does depression with current suicidal ideation lead to treatment-resistant depression? Two large naturalistic cohorts of outpatients with depression and current suicidal ideation

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## ABSTRACT

As treatment-resistant depression (TRD) is linked to suicidal behaviors and suicidal risk is a predictor of TRD, depression with current suicidal ideation (SI) may lead to TRD. Early identification of TRD risk factors in patients with depression and current SI is crucial. The aims of our study were: i) to identify risk factors for depression non-remission and TRD in patients with depression and current SI; ii) to assess if SI at baseline mediated the relationship between depression severity at baseline and depression remission at week 6. We analyzed data from two large, prospective, naturalistic French cohorts of adult outpatients with depression (DSM-IV criteria) followed for 6 weeks after starting or changing antidepressants (LUEUR and GENESE). Sociodemographic and clinical characteristics, along with early symptom improvement, were compared between patients with and without current SI using logistic regression models (univariate and multivariate). Patients with antidepressant change or initiation were analyzed separately. Those without depression remission at week 6 after an antidepressant change were considered TRD cases. In patients with antidepressant change, the major predictor of non-remission was poorer early improvement (at week 2) of anxiety. For patients with treatment initiation, SI at baseline mediated the relation between depression severity at baseline and depression remission. Depression severity at baseline alone did not explain depression remission. Clinicians should systematically target with specific pharmacological and non-pharmacological treatments anxiety and SI and assess their changes in the short term to increase the chance of depression remission in depressed patients with current SI.

## 1. Introduction

Depressive disorders are the largest contributor to non-fatal health loss (World Health Organization, 2017). As >300 million of individuals have depressive disorders worldwide (World Health Organization, 2017), these disorders represent an important cause of disability and a significant burden for the healthcare systems, the patients and their family (Arias-de la Torre et al., 2021). Despite antidepressant-based treatments, approximately one-third of patients with major depressive disorders (MDD) will progress to treatment-resistant depression (TRD) (Rush et al., 2006) (*i.e.* no response to  $\geq 2$  consecutive and adequate antidepressants used (adequate dose and duration) for the

same MDD episode, included add-on treatment, as defined by the European Medicines Agency (EMA)) (Bartova et al., 2019; EMA, 2013)).

TRD is strongly associated with suicidal behaviors (*i.e.* suicide death and suicide attempt) and is a major risk factor of suicidal behaviors. TRD is associated with higher mortality rates mainly due to the higher suicidal risk (Bergfeld et al., 2018; Gronemann et al., 2021; Orsini et al., 2022). Approximately half of patients with TRD report lifetime suicidal ideation (SI) (Orsini et al., 2022). Moreover, almost 30 % of patients with TRD will attempt suicide (*versus* 15 % of patients with non-TRD) (Bergfeld et al., 2018). In a recent nationwide study in Denmark that included >29,000 patients with TRD, TRD was associated with excess morbidity and mortality by suicide. Indeed, the risk of death by suicide

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and the risk of self-harming behavior were increased by 2.20-fold and by 1.51-fold, respectively, in patients with TRD compared with the non-TRD group (Gronemann et al., 2021). This association was not explained by depression severity. Therefore, TRD and suicide are closely related, independently of depression (Gronemann et al., 2021).

On the other hand, suicidal behaviors are predictor of TRD and some studies found that suicidal risk is an important risk factor of TRD (Balestri et al., 2016; Bennabi et al., 2015; Kautzky et al., 2019; Souery et al., 2007). Current SI has been associated with a 1.74-fold higher risk of TRD (Kautzky et al., 2019). In a study on 702 patients among whom 356 had TRD, one of the most important risk factors of TRD was current suicidal risk (2.6-fold higher risk of TRD in patients with than without current SI) (Souery et al., 2007). A recent systematic review found that SI has a stronger influence on TRD than the duration of the current depressive episode or the number of lifetime depressive episodes (1.02- and 1.15-fold higher risk of TRD, respectively) (Bennabi et al., 2015). However, not all clinicians are aware that suicidal patients are at risk of TRD. In a recent real-world survey of healthcare professionals in the United Kingdom, France, and Germany, suicidal risk was not cited as a TRD predictor, unlike the number of previous depressive episodes (Orsini et al., 2022).

Patients with depression and current SI respond less well to antidepressant treatments (Dold et al., 2018; Lopez-Castroman et al., 2016; Bénédicte Nobile et al., 2021). Recently, the European Group for the Study of Resistant Depression (GSRD) conducted a study aimed at characterizing patients with depression and current SI. They concluded that even mild/moderate SI was associated with treatment failure and, consequently, should be taken into account in clinical practice (Dold et al., 2018). Depression with current SI could be a specific subtype of depression with more severe clinical characteristics (e.g. anxiety, hopelessness), higher suicidal risk (independently of history of suicide attempt) and lower probability of remission (Batterham et al., 2019; Dold et al., 2018; Lopez-Castroman et al., 2016; B. Nobile et al., 2022; Bénédicte Nobile et al., 2021; van Ballegooijen et al., 2019). Interestingly, risk factors of depression with current SI and of TRD are similar: older age, unemployment, longer duration of the current depressive episode, higher number of previous episodes, symptom severity of the current episode (Balestri et al., 2016; Bénédicte Nobile et al., 2021).

The current therapeutic strategies for TRD and depression with SI emphasize the interest of augmentation therapies with antidepressants and antipsychotics, lithium, ketamine or esketamine. Indeed, augmentation with antipsychotics reduces depression (in patients with TRD) and SI (in patients with depression and SI) more efficiently than antidepressants alone (Reeves et al., 2008; Zhou et al., 2015). Lithium is recommended as add-on treatment in TRD (Bennabi et al., 2019) and is also efficient for preventing suicidal behavior in patients with mood disorders (Smith and Cipriani, 2017). More recently, it has been shown that ketamine and esketamine can rapidly reduce depression severity in patients with TRD and SI in patients with depression and SI (Abbar et al., 2022; Canuso et al., 2018; Kim et al., 2019; Wang et al., 2021).

These findings suggest that depression with current SI and TRD are closely related and that depression with current SI could lead to TRD. Moreover, we previously published a study that aimed to compare patients with depression and current SI to patients with depression without current SI (Bénédicte Nobile et al., 2021). Results showed that patients with depression and current SI presented worse clinical characteristics than patients with depression without current SI, among whom less remission of depression at the end of the 6 weeks of follow-up. To take early action, it is primordial to identify risk factors of TRD in patients with depression and current SI. Thus, the aims of our study were: i) to identify risk factors of depression non-remission and of TRD in patients with depression and current SI; ii) to assess if SI at baseline mediated the relation between depression severity at baseline and depression remission at week 6. To identify such risk factors, we selected only patients with depression and current SI from the same cohorts of our previous study and compared sociodemographic, clinical characteristics and

early symptom improvement (e.g. depression, anxiety) after antidepressant treatment initiation/change between patients with and without remission at week 6. We analyzed separately patients who initiated (first antidepressant for the current depressive episode) and changed antidepressant (at least second antidepressant for the current depressive episode). We considered patients with a change of antidepressant at inclusion and without depression remission at week 6 as patients with TRD, according to the depression of TRD mainly used in clinical practice and research for the current depressive episode (Yrondi et al., 2024; Zanardi et al., 2024). We also investigated whether SI mediated the relation between depression severity at baseline and depression remission. This is one of the first studies to assess risk factors for depression non-remission and TRD specifically in patients with depression and current SI. Most existing studies assess TRD risk factors in depressed patients without focusing solely on those with current SI. This is a key point of novelty, as our findings contribute to identifying early predictors of depression non-remission and TRD in such patients, which is crucial given the prevalence of SI among depressed patients and emerging evidence suggesting that patients with depression and current SI could represent a specific subtype of depression. Timely interventions are essential in this group.

## 2. Materials and methods

### 2.1. Participants' recruitment

LUEUR and GENESE are two large, prospective, naturalistic cohorts of >3000 French adult outpatients with a diagnosis of major depressive episode (MDE) according to the DSM-IV criteria, treated with antidepressants (instauration of an antidepressant or switch to another antidepressant), and followed for 6 weeks. These cohorts were created separately to explore different factors associated with MDE, suicidal behavior, and antidepressant treatment. The present study is not a post-hoc analysis from another study (Courtet et al., 2014; Voegeli et al., 2016).

General practitioners or psychiatrists recruited patients at primary and psychiatric care centers throughout France. The same physician assessed the patient at the first (baseline) and second visit (week 6). In both studies, non-inclusion criteria were: <18 years of age, bipolar disorder, schizophrenia, primary substance misuse, primary organic disease, and pregnancy or breastfeeding. Additional non-inclusion criteria in the GENESE study were: non-Caucasian ethnicity, and alcohol and substance dependence at inclusion. Additional non-inclusion criteria in the LUEUR study were: treatment with an antipsychotic or a mood stabilizer at inclusion. Add-on antipsychotic or mood stabilizer drugs prescribed by the practitioners after inclusion were allowed.

In both cohorts, participants started antidepressant treatment or changed antidepressant treatment at recruitment. In the GENESE cohort, all patients were treated with tianeptine (between 12.5 and 37.5 mg/day). In the LUEUR cohort, all patients were treated with antidepressants approved by the European Medicines Agency, although most patients received tianeptine. Of note, tianeptine was one of the most frequently prescribed antidepressants in France at enrollment time (2010) (Gusmão et al., 2013). In both cohorts, other concomitant treatments for current somatic problems, sleep or anxiety disorders were allowed based on clinical judgment. Therefore, data on associated psychotropic treatments (e.g. anxiolytics) were also collected. The study was approved by the French Medical Council and local ethics committees (Comité de Protection des Personnes CPP Ile de France XI-CPPIDF11, Centre Hospitalier Intercommunal CHI Poissy Saint-Germain, Saint Germain en Laye, reference n. 08,042) and complies with the guidelines of the Declaration of Helsinki. All patients were informed about the study aims and procedures and signed a written informed consent.

## 2.2. Clinical assessment

Demographic data, number of life time MDEs, current MDE duration, age at first MDE, lifetime history of suicide attempt and number of suicide attempts (only in the GENESE cohort) were recorded at baseline. Depression severity and SI were evaluated by clinicians at baseline and at week 6. Patients self-rated depression severity and SI at baseline, week 1, week 2 and week 6 in the LUEUR cohort, and at baseline, week 2, week 4 and week 6 in the GENESE cohort.

Depression severity was assessed with the French self-rated version of the Hospital Anxiety and Depression Scale (HADS). This scale demonstrated a good performance for assessing depression severity in psychiatric and primary care patients and a good sensitivity to change (Bjelland et al., 2002; Friedman et al., 2001). Most factor analyses found a two-factor solution in accordance with the Anxiety (HADS-A) and Depression (HADS-D) subscales. Each subscale includes seven items scored from 0 to 3 and the total score for each subscale ranges from 0 to 21. HADS-D and HADS-A sub-scores  $\geq 8$  indicate depression and anxiety, respectively. The agitation and psychic anxiety sub-scores also can be calculated (sum of items 1, 7, and 11 and sum of items 3, 5 and 13, respectively) (Lopez-Castroman et al., 2020). This scale was chosen for its simplicity of use, good comprehensibility and robust psychometric properties, demonstrated also in outpatient groups (Demyttenaere et al., 2009). In this scale, depressive symptom severity is assessed independently of any SI/suicidal behavior (no item about SI).

SI was evaluated using the suicidal item of the self- and clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS) (item number 10, or MADRS-SI). MADRS-SI score ranges from 0 to 6 (0 to 1: enjoys life or takes it as it comes; 2 to 3: weary of life, only fleeting suicidal thoughts; 4 to 5: probably better off dead, suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention; and 6: explicit plans for suicide when there is an opportunity, active preparations for suicide). A previous study showed that a single suicide item from a depression rating scale, clinician-rated or self-reported, is a valid approach to assess SI compared with the Beck's scale (Desseilles et al., 2012). This method was used in large clinical studies, such as the STAR\*D (Zisook et al., 2009), and also in more recent studies (Ballard et al., 2017; Bernert et al., 2017; B. Nobile et al., 2018). For this study, we used self-rated SI since clinicians may under evaluate SI and patients may declare more often declare SI in self-rated questionnaires than during clinical interview according to recent studies (Czyz et al., 2016; Bénédicte Nobile et al., 2023; Uhl et al., 2023).

In the LUEUR cohort, hopelessness was assessed using the self-report version of the Beck Hopelessness Scale at baseline, week 1, week 2, and week 6. This scale is valid and reliable (Kliem et al., 2018). It is composed of 20 items, and its score ranges from 0 to 20 (20 indicates the highest level of hopelessness).

In the GENESE cohort, impulsivity was assessed using the self-report version of the Plutchik's questionnaire (« *The Measurement of Emotions–1st Edition.*, 2023). This scale has good validity and reliability (Alcázar-Córcoles et al., 2015). It includes 15 items, each of which can be scored as “never” (=0), “sometimes” (=1), “often” (=2), and “almost always” (=3). The total score ranges from 0 to 45 (45 indicates the highest impulsivity). Sleep disturbances were assessed with the MADRS sleep item. Sleep disturbances and impulsivity were assessed at baseline, week 2, week 4, and week 6.

## 2.3. Definition of depression with current SI

Depression with current SI was defined as having a HADS-D sub-score  $\geq 8$  and a MADRS-SI score  $\geq 2$ .

## 2.4. Definition of depression remission

Depression remission was defined as having a HADS-D sub-score  $< 8$

at week 6. We choose this definition of depression remission since this last is the most use in clinical research and practice (Bénédicte Nobile et al., 2021; Yrondi et al., 2024; Zanardi et al., 2024).

## 2.5. Definition of early symptom improvement after antidepressant treatment initiation/change

Early improvement in depression was defined by a decrease of at least 20 % in the HADS-D sub-score at week 2. This cut-off is widely used to define the early response to treatment (Bénédicte Nobile et al., 2021; Olgiati et al., 2018; Wagner et al., 2017). The relative difference in the HADS-D sub-scores also was calculated as follows: (sub-score at week 2 – sub-score at baseline)/sub-score at baseline, as done in other studies (Bénédicte Nobile et al., 2021). Early improvement in anxiety was defined by a decrease of at least 20 % in the HADS-A sub-score at week 2. The relative difference of the HADS-A sub-scores was calculated as done for the HADS-D sub-score. The total early improvement (HADS total score) was defined as a decrease of at least 20 % in the HADS total score at week 2. The relative difference in the HADS total score also was calculated.

To assess the early improvement in other symptoms, the relative differences in the MADRS-SI, Beck Hopelessness Scale (LUEUR only) and Plutchik's questionnaire (impulsivity) (GENESE only) scores at week 2 were calculated.

## 2.6. Suicide attempts during the follow-up

For both cohorts, the occurrence of a suicide attempt during follow-up was recorded. However, due to the small number of suicide attempts in the GENESE cohort ( $N = 19$ ), only those from the LUEUR cohort were analyzed.

## 2.7. Patients' selection for analysis

Only patients with depression and current SI at inclusion and without missing data on instauration/change of antidepressant treatment at inclusion and on the HADS-D sub-score at week 6 were included in the analysis: 2449 of the 3566 patients included in the GENESE cohort (68.7 %) and 3364 of the 4845 patients included in the LUEUR cohort, (69.4 %) (Figs. 1A and 1B).

## 2.8. Statistical analysis

Categorical variables were presented with percentages and quantitative variables with means and standard deviation (SD). Univariate logistic regression models were used to evaluate the association between variables and depression non-remission. A multiple logistic regression model was performed with all pertinent variables associated with depression non-remission with a *p-value* at 0.10 in the univariate logistic regression models. As relative differences and early responses to treatment were calculated using the baseline scores, when relative differences and early responses to treatment were included in the multiple logistic regression model, the baseline scores were not included. Patients with antidepressant treatment instauration at inclusion were analyzed separately from those with antidepressant change at inclusion.

A mediation analysis was used to determine whether the effect of baseline depression level on remission at week 6 could be understood as partly or completely mediated by SI severity at baseline. The significance of direct and indirect effects was estimated with bootstrap confidence intervals based on 5000 bootstrap samples.

The significance level was set at  $p < 0.05$  for the global *p-value*. Analyses were performed with the R software (version 4.2.2).

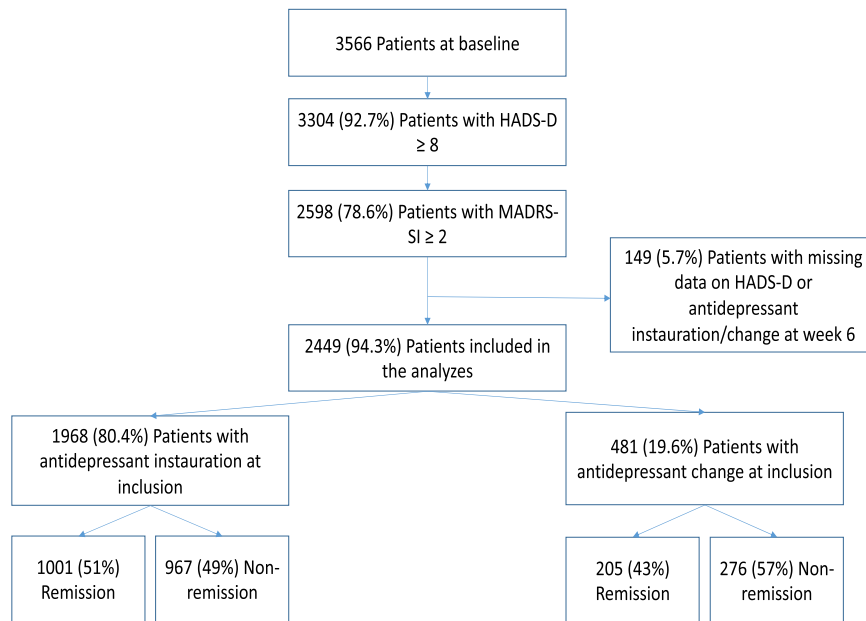


Fig. 1A. Flowchart of the selection of patients from the GENESE cohort.

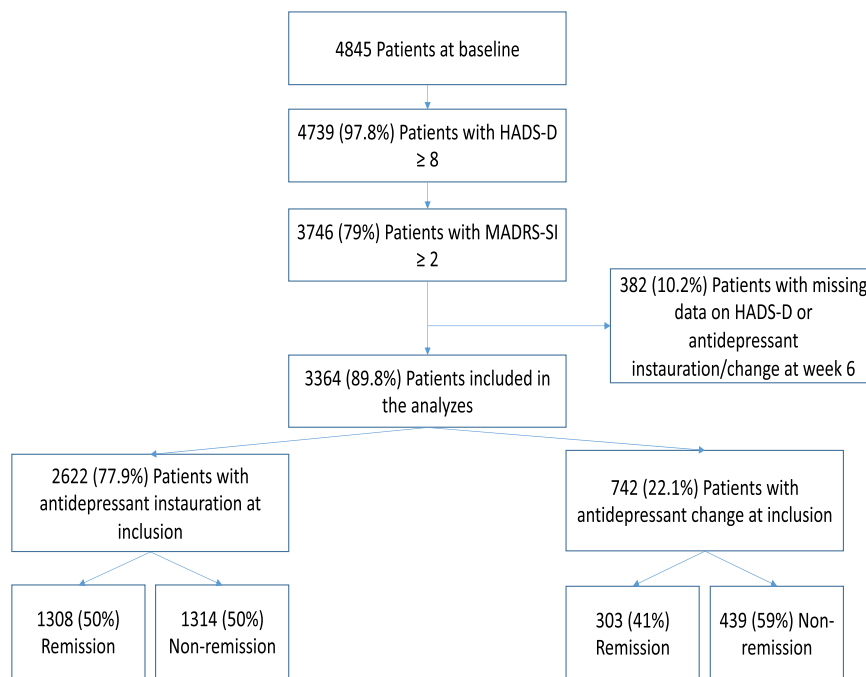


Fig. 1B. Flowchart of the selection of patients from the LUEUR cohort.

### 3. Results

#### 3.1. Description of the sample with antidepressant instauration at inclusion

In the GENESE cohort, 1968 patients started treatment with antidepressants at inclusion. They were mainly women (60 %) with a mean age of 49 (SD = 15) years and a mean HADS-D sub-score of 14.9 (SD = 3.3). At week 6, 1001 (49 %) patients did not achieve MDE remission. In the LUEUR cohort, 2622 patients started treatment with antidepressants: 62 % were women, their mean age was 47 (SD = 14) years, and their mean HADS-D sub-score was 15.6 (3.4). At week 6, 1314 (50 %) patients did not achieve MDE remission.

#### 3.2. Association between sociodemographic and clinical characteristics and depression non-remission in patients who started treatment at inclusion (Tables 1A-2B)

Compared with patients with depression remission, those without MDE remission at week 6 were significantly older, more often unemployed and with an education level below secondary school in both cohorts. In the LUEUR cohort, patients with depression non-remission were more often women and single. In both cohorts patients with depression non-remission had longer duration of the current MDE, higher number of lifetime MDEs, more frequent history of suicide attempt, and higher SI level at baseline. In the GENESE cohort, patients with depression non-remission had lower levels of depression and

**Table 1A**  
Association between sociodemographic and clinical characteristics and remission of depression in patients with antidepressant instauration at inclusion (GENESE cohort).

Variables	Remission, N = 1001 (51 %) <sup>1</sup>	Non-remission, N = 967 (49 %) <sup>1</sup>	OR <sup>2</sup>	95 % CI <sup>2</sup>	p-value
<b>Sex</b>					
Men	420 (42 %)	373 (39 %)	—	—	
Women	581 (58 %)	594 (61 %)	1.15	0.96, 1.38	0.13
<b>Age</b>	48 (15)	50 (15)	1.01	1.00, 1.01	<b>0.013</b>
<b>Education level</b>					
Secondary school	611 (61 %)	502 (52 %)	—	—	
Below secondary school	384 (39 %)	457 (48 %)	1.45	1.21, 1.73	<b>&lt;0.001</b>
<b>Professional activity</b>					
Yes	617 (62 %)	483 (50 %)	—	—	
No	376 (38 %)	478 (50 %)	1.62	1.36, 1.95	<b>&lt;0.001</b>
<b>Marital status</b>					
Not single	817 (82 %)	792 (82 %)	—	—	
Single	181 (18 %)	170 (18 %)	0.97	0.77, 1.22	0.8
<b>Current MDE duration</b>					
<2 months	383 (39 %)	329 (35 %)	—	—	
2–6 months	434 (44 %)	387 (41 %)	1.04	0.85, 1.27	0.7
>6 months	164 (17 %)	226 (24 %)	1.60	1.25, 2.06	<b>&lt;0.001</b>
<b>First MDE</b>					
No	338 (34 %)	414 (43 %)	—	—	
Yes	661 (66 %)	549 (57 %)	0.68	0.56, 0.81	<b>&lt;0.001</b>
<b>Number of lifetime MDEs</b>	0.77 (1.48)	1.08 (1.85)	1.13	1.06, 1.20	<b>&lt;0.001</b>
<b>Cumulative duration of previous MDEs (weeks)</b>	30 (25)	31 (28)	1.00	1.00, 1.01	0.7
<b>Age at first MDE (years)</b>	43 (15)	44 (16)	1.00	1.00, 1.01	0.3
<b>Lifetime SA</b>					
No	906 (93 %)	809 (87 %)	—	—	
Yes	69 (7.1 %)	123 (13 %)	2.00	1.47, 2.73	<b>&lt;0.001</b>
<b>Number of lifetime SAs</b>	1.69 (1.81)	1.68 (1.55)	1.00	0.84, 1.20	>0.9
<b>MADRS-SI score</b>	2.81 (0.96)	2.96 (1.06)	1.16	1.06, 1.27	<b>&lt;0.001</b>
<b>HADS-Depression score</b>	14.7 (3.3)	15.0 (3.2)	1.03	1.00, 1.06	<b>0.023</b>
<b>HADS-Anxiety score</b>	14.4 (3.3)	14.2 (3.5)	0.98	0.96, 1.01	0.14
<b>HADS-Agitation score</b>	6.11 (1.62)	5.96 (1.66)	0.95	0.90, 1.00	0.051
<b>HADS-Psychic anxiety score</b>	8.32 (2.29)	8.24 (2.47)	0.98	0.95, 1.02	0.4
<b>HADS total score</b>	29.1 (5.5)	29.2 (5.5)	1.00	0.99, 1.02	0.7
<b>Impulsivity score</b>	37.6 (6.2)	36.9 (6.2)	0.98	0.97, 1.00	<b>0.028</b>
<b>MADRS-Sleep score</b>					
<3	201 (20 %)	203 (21 %)	—	—	
≥3	797 (80 %)	762 (79 %)	0.95	0.76, 1.18	0.6

**Table 1A (continued)**

Variables	Remission, N = 1001 (51 %) <sup>1</sup>	Non-remission, N = 967 (49 %) <sup>1</sup>	OR <sup>2</sup>	95 % CI <sup>2</sup>	p-value
<b>Associated treatment</b>					
No	479 (48 %)	425 (44 %)	—	—	
Yes	522 (52 %)	542 (56 %)	1.17	0.98, 1.40	0.083
<b>Associated treatment (benzodiazepine)</b>					
No	495 (49 %)	445 (46 %)	—	—	
Yes	506 (51 %)	522 (54 %)	1.15	0.96, 1.37	0.13
<b>Associated treatment (mood regulator)</b>					
No	969 (97 %)	929 (96 %)	—	—	
Yes	32 (3.2 %)	38 (3.9 %)	1.24	0.77, 2.01	0.4
<b>HADS-Depression score relative difference at week 2</b>	−0.22 (0.21)	−0.10 (0.19)	28.8	16.8, 50.1	<b>&lt;0.001</b>
<b>HADS-Anxiety score relative difference at week 2</b>	−0.19 (0.20)	−0.08 (0.23)	19.2	11.4, 33.0	<b>&lt;0.001</b>
<b>HADS-Agitation score relative difference at week 2</b>	−0.47 (0.30)	−0.20 (0.36)	26.8	18.2, 40.0	<b>&lt;0.001</b>
<b>HADS-Psychic anxiety score relative difference at week 2</b>	−0.62 (0.27)	−0.26 (0.40)	80.5	52.5, 126	<b>&lt;0.001</b>
<b>HADS total score relative difference at week 2</b>	−0.21 (0.18)	−0.10 (0.16)	83.1	43.1, 164	<b>&lt;0.001</b>
<b>MADRS-SI score relative difference at week 2</b>	0.00 (0.58)	0.15 (0.61)	1.56	1.33, 1.83	<b>&lt;0.001</b>
<b>MADRS-Sleep score relative difference at week 2</b>	−0.29 (0.32)	−0.16 (0.30)	3.88	2.79, 5.45	<b>&lt;0.001</b>
<b>Impulsivity score relative difference at week 2</b>	−0.08 (0.11)	−0.03 (0.10)	98.6	36.9, 273	<b>&lt;0.001</b>
<b>Reduction of HADS-Depression score at week 2 (20 %)</b>					
Yes	512 (53 %)	245 (28 %)	—	—	
No	460 (47 %)	636 (72 %)	2.89	2.38, 3.51	<b>&lt;0.001</b>
<b>Reduction of HADS-Anxiety score at week 2 (20 %)</b>					
Yes	487 (50 %)	226 (26 %)	—	—	
No	484 (50 %)	647 (74 %)	2.88	2.37, 3.51	<b>&lt;0.001</b>
<b>Reduction of HADS total score at week 2 (20 %)</b>					
Yes	481 (50 %)	199 (23 %)	—	—	
No	485 (50 %)	664 (77 %)	3.31	2.71, 4.06	<b>&lt;0.001</b>

**Table 1B**

Association between sociodemographic and clinical characteristics and remission of depression in patients with antidepressant instauration at inclusion (LUEUR cohort).

Variables	Remission, N = 1308 (50 %) <sup>1</sup>	Non-remission, N = 1314 (50 %) <sup>1</sup>	OR <sup>2</sup>	95 % CI <sup>2</sup>	p-value
<b>Sex</b>					
Men	518 (40 %)	468 (36 %)	—	—	
Women	790 (60 %)	846 (64 %)	1.19	1.01, 1.39	<b>0.035</b>
<b>Age</b>	46 (13)	48 (15)	1.01	1.00, 1.02	<b>&lt;0.001</b>
<b>Marital status</b>					
Not single	743 (57 %)	682 (52 %)	—	—	
Single	563 (43 %)	627 (48 %)	1.21	1.04, 1.42	<b>0.014</b>
<b>Children</b>					
No	344 (27 %)	331 (25 %)	—	—	
Yes	954 (73 %)	971 (75 %)	1.06	0.89, 1.26	0.5
<b>Living alone</b>					
No	828 (64 %)	817 (63 %)	—	—	
Yes	464 (36 %)	483 (37 %)	1.05	0.90, 1.24	0.5
<b>Education level</b>					
Secondary school	828 (64 %)	739 (57 %)	—	—	
Below secondary school	465 (36 %)	567 (43 %)	1.37	1.17, 1.60	<b>&lt;0.001</b>
<b>Professional activity</b>					
Yes	786 (63 %)	682 (55 %)	—	—	
No	455 (37 %)	567 (45 %)	1.44	1.22, 1.69	<b>&lt;0.001</b>
<b>Current MDE duration (weeks)</b>	6.3 (7.8)	7.2 (10.1)	1.01	1.00, 1.02	<b>0.012</b>
<b>Number of lifetime MDEs</b>	1.06 (4.65)	1.53 (6.27)	1.02	1.00, 1.04	<b>0.05</b>
<b>Age at first MDE</b>	39 (14)	40 (15)	1.00	1.00, 1.01	0.3
<b>Associated treatment</b>					
None	1 147 (89 %)	1 076 (84 %)	—	—	
Antidepressant	7 (0.5 %)	5 (0.4 %)	0.76	0.22, 2.39	0.6
Neuroleptic	74 (5.7 %)	114 (8.9 %)	1.64	1.21, 2.23	<b>0.001</b>
Mood regulator	59 (4.6 %)	87 (6.8 %)	1.57	1.12, 2.22	<b>0.009</b>
<b>Antidepressant type</b>					
More than one	7 (0.6 %)	5 (0.5 %)	—	—	
Other	61 (5.3 %)	65 (6.0 %)	1.49	0.45, 5.28	0.5
IRSNA	48 (4.2 %)	46 (4.3 %)	1.34	0.40, 4.82	0.6
ISRS	50 (4.3 %)	48 (4.4 %)	1.34	0.40, 4.81	0.6
Tianeptine	988 (86 %)	917 (85 %)	1.3	0.41, 4.40	0.7
<b>Antidepressant type (binary)</b>					
Other	166 (14 %)	164 (15 %)	—	—	
Tianeptine	988 (86 %)	917 (85 %)	0.94	0.74, 1.19	0.6
<b>Alcohol use disorder</b>					
No	1 243 (96 %)	1 219 (93 %)	—	—	
Yes	58 (4.5 %)	90 (6.9 %)	1.58	1.13, 2.23	<b>0.008</b>
<b>Lifetime SA</b>					
No	1 104 (85 %)	1 034 (79 %)	—	—	
Yes	196 (15 %)	278 (21 %)	1.51	1.24, 1.85	<b>&lt;0.001</b>
<b>MADRS-SI score</b>	2.75 (0.86)	2.90 (0.96)	1.20	1.10, 1.31	<b>&lt;0.001</b>

**Table 1B (continued)**

Variables	Remission, N = 1308 (50 %) <sup>1</sup>	Non-remission, N = 1314 (50 %) <sup>1</sup>	OR <sup>2</sup>	95 % CI <sup>2</sup>	p-value
<b>HADS-Anxiety score</b>	14.8 (3.2)	14.7 (3.3)	0.99	0.97, 1.01	0.5
<b>HADS-Depression score</b>	15.5 (3.4)	15.7 (3.3)	1.02	1.00, 1.04	0.1
<b>HADS-Agitation score</b>	7.01 (1.31)	7.10 (1.32)	1.05	0.99, 1.11	0.094
<b>HADS-Psychic anxiety score</b>	8.31 (1.43)	8.26 (1.52)	0.97	0.93, 1.03	0.3
<b>HADS total score</b>	30.3 (5.5)	30.4 (5.6)	1	0.99, 1.02	0.6
<b>Hopelessness score</b>	16.7 (3.0)	16.5 (3.2)	0.98	0.96, 1.01	0.15
<b>SA during the follow-up</b>					
No	1 220 (99 %)	1 241 (97 %)	—	—	
Yes	7 (0.6 %)	34 (2.7 %)	4.77	2.24, 11.8	<b>&lt;0.001</b>
<b>HADS-Depression score relative difference at week 2</b>	-0.34 (0.21)	-0.18 (0.18)	76.7	47.3, 126	<b>&lt;0.001</b>
<b>HADS-Anxiety score relative difference at week 2</b>	-0.30 (0.21)	-0.16 (0.19)	42.4	26.3, 69.0	<b>&lt;0.001</b>
<b>HADS-Agitation score relative difference at week 2</b>	0.13 (0.22)	0.08 (0.19)	0.29	0.19, 0.43	<b>&lt;0.001</b>
<b>HADS-Psychic anxiety score relative difference at week 2</b>	0.19 (0.21)	0.11 (0.21)	0.18	0.12, 0.27	<b>&lt;0.001</b>
<b>MADRS- SI score relative difference at week 2</b>	-0.47 (0.29)	-0.29 (0.28)	8.39	6.18, 11.5	<b>&lt;0.001</b>
<b>Hopelessness score relative difference at week 2</b>	-0.39 (0.29)	-0.15 (0.26)	25.6	17.9, 37.1	<b>&lt;0.001</b>
<b>Reduction of HADS-Depression score at week 2 (20 %)</b>					
Yes	936 (77 %)	540 (45 %)	—	—	
No	282 (23 %)	647 (55 %)	3.98	3.34, 4.74	<b>&lt;0.001</b>
<b>Reduction of HADS-Anxiety score at week 2 (20 %)</b>					
Yes	879 (72 %)	503 (42 %)	—	—	
No	343 (28 %)	685 (58 %)	3.49	2.95, 4.14	<b>&lt;0.001</b>
<b>Reduction of HADS total score at week 2 (20 %)</b>					
Yes	924 (76 %)	515 (44 %)	—	—	
No	287 (24 %)	662 (56 %)	4.14	3.48, 4.94	<b>&lt;0.001</b>

impulsivity than patients with depression remission. In the LUEUR cohort, alcohol use disorder and add-on neuroleptic or mood stabilizer at inclusion were more frequent in patients with depression non-remission. In both cohorts, no significant between-group difference was detected for age at first MDE and baseline anxiety, hopelessness, and sleep disturbances. In the LUEUR cohort, the prescribed antidepressant types were not different between groups (with and without remission).

At week 2 of treatment, depression non-remission was significantly



**Table 2A**

Association between sociodemographic and clinical characteristics and remission of depression in patients with antidepressant instauration at inclusion, multivariate analysis (GENESE cohort).

Variables	OR <sup>1</sup>	95 % CI <sup>1</sup>	p-value
<b>Age</b>	1.00	0.99 – 1.00	0.308
<b>Education level</b>			
Secondary school	—	—	
Below secondary school	1.30	1.02 – 1.65	<b>0.034</b>
<b>Professional activity</b>			
Yes			
No	1.46	1.14 – 1.87	<b>0.003</b>
<b>Current MDE duration</b>			
< 2 months			
2–6 months	0.94	0.73 – 1.20	0.624
> 6 months	1.33	0.97 – 1.82	0.072
<b>First MDE</b>			
No	—	—	
Yes	0.83	0.65 – 1.06	0.131
<b>Lifetime SA</b>			
No	—	—	
Yes	1.55	1.03 – 2.34	<b>0.036</b>
<b>Associated treatment</b>			
No	—	—	
Yes	1.08	0.86 – 1.35	0.513
<b>MADRS-SI score relative difference at week 2</b>	1.19	0.94 – 1.49	0.142
<b>MADRS-Sleep score relative difference at week 2</b>	1.69	1.07 – 2.69	<b>0.025</b>
<b>Impulsivity score relative difference at week 2</b>	10.72	3.37 – 35.02	<b>&lt;0.001</b>
<b>Reduction of HADS-Depression score at week 2 (20 %)</b>			
Yes	—	—	
No	1.79	1.40 – 2.30	<b>&lt;0.001</b>
<b>Reduction of HADS-Anxiety score at week 2 (20 %)</b>			
Yes	—	—	
No	1.89	1.46 – 2.43	<b>&lt;0.001</b>

<sup>1</sup> OR = Odds Ratio, CI = Confidence Interval.

associated with smaller improvement in all clinical variables assessed (depression, anxiety, impulsivity, sleep disturbances, hopelessness, and SI) in both cohorts. In the LUEUR cohort, depression non-remission at week 2 was associated with higher risk of suicide attempt during the follow-up.

In the multivariate models, in the LUEUR cohort, lower education level and history of suicide attempt were associated with depression non-remission at week 6. In both cohorts, lower improvement at week 2 of depression, anxiety, hopelessness, impulsivity, sleep disturbances was strongly associated with depression non-remission at week 6. For example, decreases <20 % in the HADS-D and HADS-A sub-scores were associated with a 1.79- and 1.89-fold higher risk of depression non-remission at week 6 (*p-value* < 0.001) in the GENESE cohort and with a 2.04- and 1.59-fold higher risk of depression non-remission at week 6 (*p-value* < 0.001) in the LUEUR cohort. In addition, in the LUEUR cohort, a smaller relative difference of MADRS-SI score at week 2 was strongly associated with depression non-remission (OR = 2.34; 95 % CI = 1.56–3.53, *p-value* < 0.001).

### 3.3. Description of the sample with antidepressant change at inclusion

In the GENESE cohort, 481 patients changed antidepressant molecule at inclusion. They were mainly women (68 %) with a mean age of 52 (SD = 14) years and a mean HADS-D sub-score of 14.9 (SD = 3.2). At week, 276 (57 %) patients did not achieve depression remission (*i.e.* progressed to TRD). In the LUEUR cohort, 742 patients changed antidepressant molecule at inclusion: 69 % were women, their mean age was 49 (SD = 13) years, and their mean HADS-D sub-score was 16.3 (3.3). At week 6, 439 (59 %) patients did not achieve depression remission (*i.e.* progressed to TRD).

**Table 2B**

Association between sociodemographic and clinical characteristics and remission of depression in patients with antidepressant instauration at inclusion, multivariate analysis (LUEUR cohort).

Variables	OR <sup>1</sup>	95 % CI <sup>1</sup>	p-value
<b>Age</b>	1.01	1.00 – 1.02	<b>0.025</b>
<b>Sex</b>			
Men	—	—	
Women	1.20	0.97 – 1.49	0.10
<b>Marital status</b>			
Not single	—	—	
Single	1.28	1.04 – 1.58	<b>0.020</b>
<b>Education level</b>			
Secondary school	—	—	
Below secondary school	1.33	1.07 – 1.67	<b>0.011</b>
<b>Professional activity</b>			
Yes	—	—	
No	0.95	0.75 – 1.20	0.7
<b>Current MDE duration</b>	1.01	0.99 – 1.02	0.3
<b>Number of lifetime MDEs</b>	1.03	1.01 – 1.09	0.055
<b>Associated treatment</b>			
None	—	—	
Antidepressant	1.37	0.29 – 6.37	0.7
Neuroleptic	1.52	1.01 – 2.30	<b>0.045</b>
Mood regulator	1.40	0.89 – 2.21	0.14
<b>Alcohol use disorder</b>			
No	—	—	
Yes	1.63	1.05 – 2.55	<b>0.031</b>
<b>Lifetime SA</b>			
No	—	—	
Yes	1.53	1.17 – 2.02	<b>0.002</b>
<b>HADS-Depression score reduction at week 2 (20 %)</b>			
Yes	—	—	
No	2.04	1.60 – 2.59	<b>&lt;0.001</b>
<b>HADS-Anxiety score reduction at week 2 (20 %)</b>			
Yes	—	—	
No	1.59	1.26 – 2.01	<b>&lt;0.001</b>
<b>Hopelessness score relative difference at week 2</b>	7.00	4.40 – 11.3	<b>&lt;0.001</b>
<b>MADRS-SI score relative difference at week 2</b>	2.34	1.56 – 3.53	<b>&lt;0.001</b>

<sup>1</sup> OR = Odds Ratio, CI = Confidence Interval.

### 3.4. Associations between sociodemographic and clinical characteristics and depression non-remission in patients with antidepressant change at inclusion (Tables 3A-4B)

In the GENESE cohort, sociodemographic characteristics were not significantly different between groups (with and without remission), but for marital status (*i.e.* patients with depression non-remission were more often in a relationship). In the LUEUR cohort, depression non-remission was associated with older age and lower education level.

Concerning the baseline clinical characteristics, depression, anxiety, and SI levels were not different between groups in the GENESE cohort. In the LUEUR cohort, patients with depression non-remission had longer duration of the current MDE, more frequent history of suicide attempt, and higher levels of depression and anxiety at baseline than patients with remission. Add-on treatments (both cohorts) and antidepressant type (LUEUR cohort) were not different between groups.



**Table 3A**  
Association between sociodemographic and clinical characteristics and remission of depression in patients with antidepressant change at inclusion (GENESE cohort).

Variables	Remission, N = 205 (43 %) <sup>1</sup>	Non-remission, N = 276 (57 %) <sup>1</sup>	OR2	95 % CI2	p-value
<b>Sex</b>					
Men	64 (31 %)	90 (33 %)	—	—	
Women	141 (69 %)	186 (67 %)	0.94	0.64, 1.38	0.7
<b>Age</b>	51 (13)	52 (14)	1	0.99, 1.02	0.5
<b>Education level</b>					
Secondary school	95 (46 %)	111 (41 %)	—	—	
Below secondary school	110 (54 %)	163 (59 %)	1.27	0.88, 1.83	0.2
<b>Professional activity</b>					
Yes	89 (44 %)	98 (36 %)	—	—	
No	115 (56 %)	175 (64 %)	1.38	0.95, 2.00	0.088
<b>Marital status</b>					
Not single	159 (78 %)	233 (85 %)	—	—	
Single	46 (22 %)	42 (15 %)	0.62	0.39, 0.99	<b>0.046</b>
<b>Current MDE duration</b>					
<2 months	32 (16 %)	38 (14 %)	—	—	
2–6 months	87 (44 %)	91 (34 %)	0.88	0.50, 1.53	0.7
>6 months	79 (40 %)	142 (52 %)	1.51	0.88, 2.61	0.14
<b>First MDE</b>					
No	151 (74 %)	208 (75 %)	—	—	
Yes	54 (26 %)	68 (25 %)	0.91	0.60, 1.39	0.7
<b>Number of lifetime MDEs</b>	2.8 (4.6)	3.0 (3.5)	1.01	0.97, 1.07	0.6
<b>Cumulative duration of previous MDEs (weeks)</b>	36 (30)	43 (31)	1.01	1.00, 1.02	0.064
<b>Age at first MDE (years)</b>	39 (15)	40 (16)	1.01	0.99, 1.02	0.3
<b>Lifetime SA</b>					
No	153 (75 %)	201 (73 %)	—	—	
Yes	52 (25 %)	73 (27 %)	1.07	0.71, 1.62	0.8
<b>Number of lifetime SAs</b>	1.90 (1.64)	1.60 (1.27)	0.86	0.66, 1.10	0.2
<b>MADRS-SI score</b>	3.00 (1.00)	3.14 (1.07)	1.14	0.96, 1.37	0.13
<b>HADS-Depression score</b>	14.8 (3.3)	15.0 (3.1)	1.02	0.97, 1.08	0.4
<b>HADS-Anxiety score</b>	14.7 (3.4)	14.4 (3.5)	0.98	0.93, 1.03	0.5
<b>HADS-Agitation score</b>	6.05 (1.68)	5.69 (1.83)	0.89	0.80, 0.99	<b>0.028</b>
<b>HADS-Psychic anxiety score</b>	8.62 (2.35)	8.75 (2.43)	1.02	0.95, 1.10	0.6
<b>HADS total score</b>	29.4 (5.3)	29.5 (5.2)	1	0.97, 1.04	>0.9
<b>Impulsivity score</b>	37 (6)	37 (6)	0.98	0.95, 1.01	0.2
<b>MADRS-Sleep score</b>					
<3	49 (24 %)	63 (23 %)	—	—	
≥3	155 (76 %)	209 (77 %)	1.05	0.68, 1.61	0.8
<b>Associated treatment</b>					
No	51 (25 %)	64 (23 %)	—	—	
Yes	154 (75 %)	212 (77 %)	1.1	0.72, 1.67	0.7

**Table 3A (continued)**

Variables	Remission, N = 205 (43 %) <sup>1</sup>	Non-remission, N = 276 (57 %) <sup>1</sup>	OR2	95 % CI2	p-value
<b>Associated treatment (benzodiazepine)</b>					
No	56 (27 %)	79 (29 %)	—	—	
Yes	149 (73 %)	197 (71 %)	0.94	0.62, 1.40	0.8
<b>Associated treatment (mood regulator)</b>					
No	184 (90 %)	240 (87 %)	—	—	
Yes	21 (10 %)	36 (13 %)	1.31	0.75, 2.36	0.3
<b>HADS-Depression score relative difference at week 2</b>	−0.21 (0.21)	−0.09 (0.20)	21	7.69, 61.4	<b>&lt;0.001</b>
<b>HADS-Anxiety score relative difference at week 2</b>	−0.14 (0.69)	−0.03 (0.23)	3.87	1.67, 9.46	<b>0.002</b>
<b>HADS-Agitation score relative difference at week 2</b>	−0.48 (0.28)	−0.10 (0.40)	65.5	28.6, 161	<b>&lt;0.001</b>
<b>HADS- Psychic anxiety score relative difference at week 2</b>	−0.60 (0.25)	−0.21 (0.35)	163	63.8, 457	<b>&lt;0.001</b>
<b>HADS total score relative difference at week 2</b>	−0.20 (0.18)	−0.07 (0.17)	108	29.9, 433	<b>&lt;0.001</b>
<b>MADRS-SI score relative difference at week 2</b>	−0.06 (0.56)	0.08 (0.68)	1.44	1.06, 1.97	<b>0.021</b>
<b>MADRS-Sleep score relative difference at week 2</b>	−0.27 (0.33)	−0.18 (0.36)	2.11	1.19, 3.87	<b>0.013</b>
<b>Impulsivity score relative difference at week 2</b>	−0.08 (0.11)	−0.03 (0.10)	67.7	9.54, 539	<b>&lt;0.001</b>
<b>Reduction of HADS-Depression score at week 2 (20 %)</b>					
Yes	96 (49 %)	66 (26 %)	—	—	
No	100 (51 %)	189 (74 %)	2.75	1.85, 4.10	<b>&lt;0.001</b>
<b>Reduction of HADS-Anxiety score at week 2 (20 %)</b>					
Yes	93 (47 %)	45 (18 %)	—	—	
No	104 (53 %)	209 (82 %)	4.15	2.73, 6.41	<b>&lt;0.001</b>
<b>Reduction of HADS total score at week 2 (20 %)</b>					
Yes	93 (48 %)	40 (16 %)	—	—	
No	101 (52 %)	211 (84 %)	4.86	3.15, 7.60	<b>&lt;0.001</b>

Absent/small early (week 2) symptom improvement (*i.e.* depression, anxiety, SI, sleep disturbances, impulsivity and hopelessness) was associated with depression non-remission in both cohorts. In the LUEUR cohort, depression non-remission was not associated with higher risk of suicide attempt during the follow-up.

In the multivariate analysis, smaller early improvement in anxiety, SI, sleep disturbances and hopelessness at week 2 was associated with

**Table 3B**

Association between sociodemographic and clinical characteristics and remission of depression in patients with antidepressant change at inclusion (LUEUR cohort).

Variables	Remission, N = 303 (41 %)¹	Non-remission, N = 439 (59 %)¹	OR²	95 % CI²	p-value
<b>Sex</b>					
Men	90 (30 %)	141 (32 %)	—	—	
Women	213 (70 %)	298 (68 %)	0.89	0.65, 1.23	0.5
<b>Age</b>	47 (13)	50 (13)	1.02	1.01, 1.03	<0.001
<b>Marital status</b>					
Not single	153 (50 %)	211 (48 %)	—	—	
Single	150 (50 %)	226 (52 %)	1.09	0.81, 1.47	0.6
<b>Children</b>					
No	74 (24 %)	95 (22 %)	—	—	
Yes	229 (76 %)	336 (78 %)	1.14	0.81, 1.62	0.5
<b>Living alone</b>					
No	190 (63 %)	256 (59 %)	—	—	
Yes	111 (37 %)	175 (41 %)	1.17	0.86, 1.59	0.3
<b>Education level</b>					
Secondary school	185 (61 %)	215 (50 %)	—	—	
Below secondary school	117 (39 %)	217 (50 %)	1.6	1.19, 2.15	0.002
<b>Professional activity</b>					
Yes	141 (49 %)	157 (37 %)	—	—	
No	148 (51 %)	268 (63 %)	1.63	1.20, 2.20	0.002
<b>Current MDE duration (weeks)</b>	8 (7)	12 (18)	1.03	1.02, 1.06	<0.001
<b>Number of lifetime MDEs</b>	2.35 (5.56)	3.84 (12.04)	1.02	1.00, 1.05	0.077
<b>Age at first MDE</b>	35 (12)	37 (14)	1.01	1.00, 1.02	0.2
<b>Associated treatment</b>					
None	193 (68 %)	279 (68 %)	—	—	
Antidepressant	26 (9.2 %)	25 (6.1 %)	0.67	0.37, 1.19	0.2
Neuroleptic	43 (15 %)	75 (18 %)	1.21	0.80, 1.84	0.4
Mood regulator	22 (7.7 %)	33 (8.0 %)	1.04	0.59, 1.86	0.9
<b>Antidepressant type</b>					
More than one	26 (12 %)	25 (8.2 %)	—	—	
Other	28 (13 %)	24 (7.9 %)	0.89	0.41, 1.93	0.8
IRSNA	20 (9.1 %)	37 (12 %)	1.92	0.89, 4.21	0.1
ISRS	11 (5.0 %)	14 (4.6 %)	1.32	0.51, 3.52	0.6
Tianeptine	134 (61 %)	204 (67 %)	1.58	0.88, 2.87	0.13
<b>Antidepressant type (binary)</b>					
Other	85 (39 %)	100(33 %)	—	—	
Tianeptine	134 (61 %)	204 (67 %)	1.29	0.90 – 1.86	0,2
<b>Alcohol use disorder</b>					
No	287 (95 %)	399 (91 %)	—	—	
Yes	16 (5.3 %)	39 (8.9 %)	1.75	0.98, 3.28	0.067
<b>Lifetime SA</b>					
No	198 (66 %)	245 (56 %)	—	—	
Yes	104 (34 %)	192 (44 %)	1.49	1.10, 2.02	0.01
<b>MADRS-SI score</b>	2.98 (0.99)	3.23 (1.05)	1.27	1.10, 1.47	0.001

**Table 3B (continued)**

Variables	Remission, N = 303 (41 %)¹	Non-remission, N = 439 (59 %)¹	OR²	95 % CI²	p-value
<b>HADS-Anxiety score</b>	14.7 (3.5)	15.3 (3.4)	1.06	1.01, 1.11	<b>0.009</b>
<b>HADS-Depression score</b>	15.7 (3.4)	16.7 (3.2)	1.1	1.05, 1.15	<b>&lt;0.001</b>
<b>HADS-Agitation score</b>	7.13 (1.40)	7.17 (1.43)	1.02	0.92, 1.13	0.7
<b>HADS-Psychic anxiety score</b>	8.33 (1.54)	8.07 (1.48)	0.89	0.81, 0.98	<b>0.024</b>
<b>HADS total score</b>	30.4 (5.4)	32.1 (5.4)	1.06	1.03, 1.09	<b>&lt;0.001</b>
<b>Hopelessness score</b>	16.4 (3.5)	16.9 (3.3)	1.04	0.99, 1.09	0.09
<b>SA during the follow-up</b>					
No	272 (97 %)	409 (96 %)	—	—	
Yes	9 (3.2 %)	19 (4.4 %)	1.4	0.64, 3.30	0.4
<b>HADS-Depression score relative difference at week 2</b>	-0.33 (0.23)	-0.17 (0.17)	89.6	35.2, 242	<b>&lt;0.001</b>
<b>HADS-Anxiety score relative difference at week 2</b>	-0.29 (0.20)	-0.14 (0.20)	55.6	22.7, 143	<b>&lt;0.001</b>
<b>HADS-Agitation score relative difference at week 2</b>	0.11 (0.20)	0.08 (0.21)	0.5	0.24, 1.06	0.073
<b>HADS-Psychic anxiety score relative difference at week 2</b>	0.19 (0.20)	0.10 (0.22)	0.14	0.06, 0.29	<b>&lt;0.001</b>
<b>MADRS-SI score relative difference at week 2</b>	-0.45 (0.30)	-0.24 (0.31)	11.7	6.52, 21.4	<b>&lt;0.001</b>
<b>Hopelessness score relative difference at week 2</b>	-0.38 (0.31)	-0.13 (0.27)	22.9	11.8, 46.3	<b>&lt;0.001</b>
<b>HADS-Depression score reduction at week 2 (20 %)</b>					
Yes	215 (76 %)	175 (44 %)	—	—	
No	69 (24 %)	219 (56 %)	3.9	2.80, 5.48	<b>&lt;0.001</b>
<b>HADS-Anxiety score reduction at week 2 (20 %)</b>					
Yes	198 (69 %)	141 (36 %)	—	—	
No	87 (31 %)	250 (64 %)	4.04	2.92, 5.61	<b>&lt;0.001</b>
<b>HADS total score reduction at week 2 (20 %)</b>					
Yes	212 (75 %)	143 (37 %)	—	—	
No	71 (25 %)	246 (63 %)	5.14	3.68, 7.24	<b>&lt;0.001</b>

depression non-remission at week 6 in both cohorts, but not in depression (both cohorts) and impulsivity (LUEUR cohort). Indeed, in both cohorts, reduction of the HADS-D sub-score by <20 % at week 2 was not associated with depression non-remission. Conversely, HADS-A sub-score decrease by <20 % was associated with depression non-remission (OR = 3.08; 95 % CI = 1.85–5.18, p-value < 0.001 in the GENESE cohort and OR = 1.83; 95 % CI = 1.17–2.86, p-value = 0.008 in the LUEUR cohort). In the LUEUR cohort, the relative differences of the MADRS-SI

**Table 4A**

Association between sociodemographic and clinical characteristics and remission of depression in patients with antidepressant change at inclusion, multivariate analysis (GENESE cohort).

Variables	OR <sup>1</sup>	95 % CI <sup>1</sup>	p-value
<b>Marital status</b>			
Not single	—	—	
Single	0.85	0.47 – 1.55	0.590
<b>Professional activity</b>			
Yes			
No	1.29	0.81 – 2.05	0.277
MADRS-SI score relative difference at week 2	1.18	0.76 – 1.84	0.462
MADRS-Sleep score relative difference at week 2	0.84	0.37 – 1.98	0.692
Impulsivity score relative difference at week 2	8.75	0.83 – 100.99	0.076
<b>HADS-Depression score reduction at week 2 (20 %)</b>			
Yes	—	—	
No	1.57	0.93 – 2.62	0.086
<b>HADS-Anxiety score reduction at week 2 (20 %)</b>			
Yes	—	—	
No	3.08	1.85 – 5.18	<0.001

<sup>1</sup> OR = Odds Ratio, CI = Confidence Interval.

**Table 4B**

Association between sociodemographic and clinical characteristics and remission of depression in patients with antidepressant change at inclusion, multivariate analysis (LUEUR cohort).

Variables	OR <sup>1</sup>	95 % CI <sup>1</sup>	p-value
<b>Age</b>	1.01	0.99 – 1.02	0.5
<b>Study level</b>			
Secondary school	—	—	
Below secondary school	1.22	0.81 – 1.83	0.3
<b>Professional activity</b>			
Yes	—	—	
No	1.17	0.76 – 1.78	0.5
<b>Current MDE duration (weeks)</b>	1.02	1.0 – 1.04	0.2
<b>Number of lifetime MDEs</b>	1.02	1.00 – 1.07	0.13
<b>Alcohol dependence</b>			
No	—	—	
Yes	1.12	0.51 – 2.60	0.8
<b>Lifetime SA</b>			
No	—	—	
Yes	1.27	0.85 – 1.92	0.2
<b>HADS-Depression score reduction at week 2 (20 %)</b>			
Yes	—	—	
No	1.43	0.90 – 2.27	0.13
<b>HADS-Anxiety score reduction at week 2 (20 %)</b>			
Yes	—	—	
No	1.83	1.17 – 2.86	0.008
<b>MADRS-SI score relative difference at week 2</b>	2.93	1.37 – 6.37	0.006
<b>Hopelessness score relative difference at week 2</b>	5.33	2.21 – 13.3	<0.001

<sup>1</sup> OR = Odds Ratio, CI = Confidence Interval.

and Hopelessness scores at week 2 were associated with depression non-remission (OR = 2.93; 95 % CI = 1.37–6.37, *p-value* = 0.006 and OR = 5.33; 95 % CI = 2.21–13.3, *p-value* < 0.001, respectively).

Table 5 lists all variables associated with depression non-remission in patients who started or changed treatment at inclusion (both cohorts).

**Table 5**

Summary of variables associated with depression non-remission in patients who started or changed treatment at inclusion.

<i>Antidepressant instauration at inclusion</i>	
GENESE	LUEUR
	More often women
Older	<b>Older</b>
<b>Below secondary school</b>	<b>Below secondary school</b>
<b>No employment</b>	No employment
	<b>More often single</b>
Longer current MDE duration	Longer current MDE duration
Higher number of MDEs	Higher number of MDEs
	More often associated mood stabilizer or neuroleptic drug
	<b>More often alcohol use disorder</b>
	<b>More often history of suicide attempt</b>
<b>More often history of suicide attempt</b>	MADRS-SI score at inclusion
Higher MADRS-SI score at inclusion	
Lower depression level at inclusion	
Lower impulsivity level at inclusion	
<b>Smaller HADS-Depression score reduction at week 2</b>	<b>Smaller HADS-Depression score reduction at week 2</b>
<b>Smaller HADS-Anxiety score reduction at week 2</b>	<b>Smaller HADS-Anxiety score reduction at week 2</b>
<b>Smaller Impulsivity score reduction at week 2</b>	
<b>Smaller decrease of sleep disturbances at week 2</b>	
Smaller decrease of SI at week 2	<b>Smaller decrease of SI at week 2</b>
	<b>Smaller decrease of hopelessness at week 2</b>
	Higher risk of suicide attempt during the follow-up
<b>Change of antidepressant at inclusion</b>	
<b>GENESE</b>	<b>LUEUR</b>
More often in relationship	
	Older
	Below secondary school
	Longer current MDE duration
	More often history of suicide attempt
	Higher depression level at inclusion
	Higher anxiety level at inclusion
Lower agitation level at inclusion	
Smaller decrease of depression level at week 2	Smaller decrease of depression level at week 2
<b>Smaller decrease of anxiety level at week 2</b>	<b>Smaller decrease of anxiety level at week 2</b>
Smaller decrease of impulsivity level at week 2	
Smaller decrease of sleep disturbances at week 2	
Smaller decrease of SI at week 2	<b>Smaller decrease of SI at week 2</b>
	<b>Smaller decrease of hopelessness at week 2</b>

\*Bold indicates significant variables in multivariate models.

3.5. Mediation analysis

The depression level at baseline had an effect on remission through SI only in patients with first treatment instauration; however, baseline depression severity alone did not explain depression remission at week 6 (*i.e.* direct effect not significant and indirect effect significant) (Fig. 2A, B). This indirect effect represented 31 % and 77 % of the total effect in the GENESE cohort and in the LUEUR cohort, respectively. For patients with treatment change, SI did not mediate the relation between depression severity at baseline and depression remission at week 6. Moreover, in the LUEUR cohort, but nor in the GENESE cohort, depression severity at baseline had a direct effect on depression remission (Fig. 3A,B).

4. Discussion

To our knowledge, this is the first study that identified risk factors of depression non-remission and of TRD in two large naturalistic cohorts of

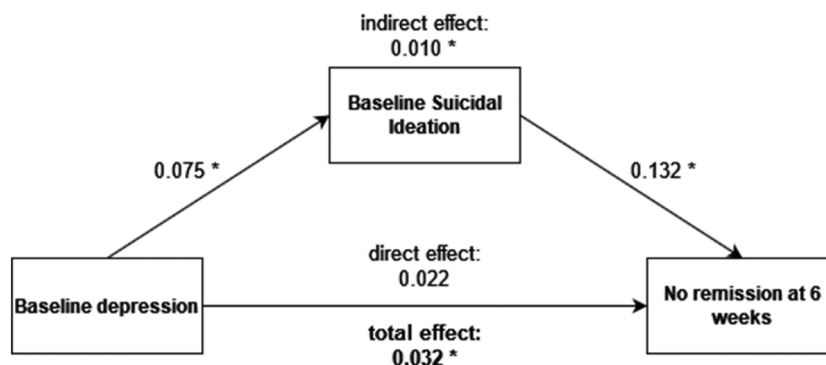


Fig. 2A. Mediation analysis for patients with treatment instauration (GENESE cohort).

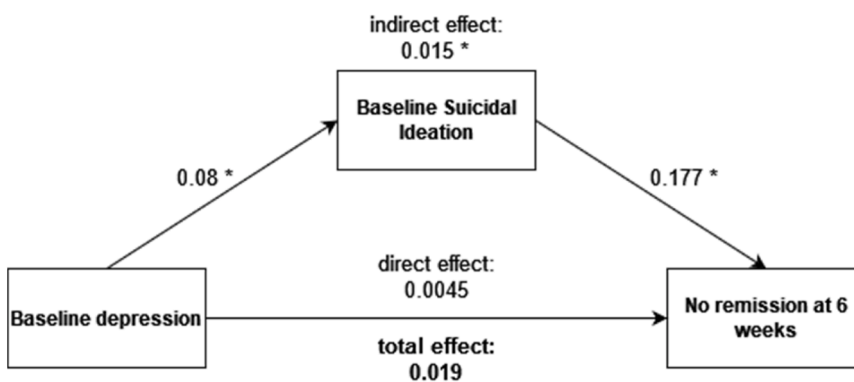


Fig. 2B. Mediation analysis for patients with treatment instauration (LUEUR cohort).

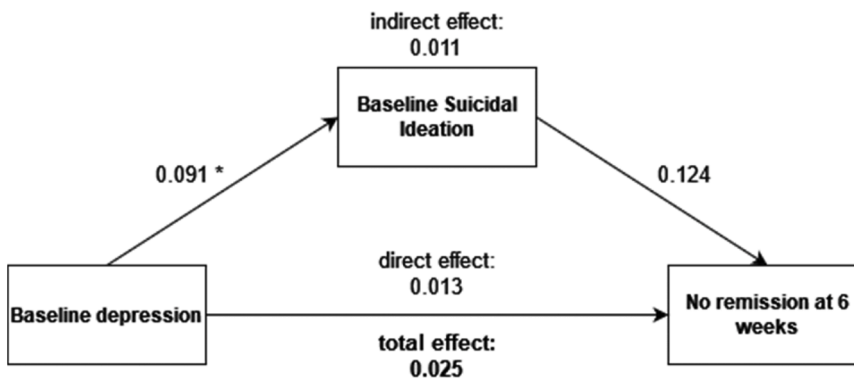


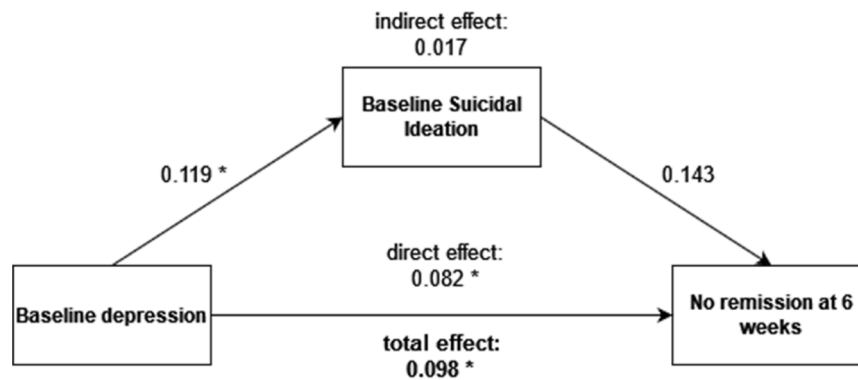
Fig. 3A. Mediation analysis for patients with treatment change (GENESE cohort).

patients with depression with current SI. Depressed patients with current SI who started (*i.e.* first antidepressant for the current MDE) and changed (*i.e.* at least second antidepressant for the current MDE) antidepressant treatment at baseline were analyzed separately. Almost 50 % and 60 % of patients with first antidepressant treatment and with antidepressant change at inclusion, respectively, did not achieve depression remission at week 6.

Risk factors of depression non-remission were different in patients with instauration or change of antidepressant treatment at inclusion. In patients with antidepressant instauration at inclusion, the main factors associated with depression non-remission were low education level, history of suicide attempt, and limited symptom improvement at week 2. Non-early improvement of symptomatology at week 2 was the factor most strongly associated with depression non-remission. This concerned not only depression. Indeed, non-improvement at week 2 of anxiety, hopelessness, impulsivity, and SI scores also strongly predicted

depression non-remission. This suggests that targeting only depression in depressed patients with current SI is not sufficient to obtain depression remission, as proposed by other studies (Bénédicte Nobile et al., 2020, 2021). In clinical practice, clinicians assess the response to treatment mainly by monitoring depression levels (Olgiatei et al., 2018). However, they should systematically assess also other MDE dimensions, such as anxiety, hopelessness, and impulsivity, which are strongly associated with high suicidal risk (Coryell et al., 2018; De La Vega et al., 2018; Bénédicte Nobile et al., 2021; Ribeiro et al., 2018). Moreover, we found that patients with depression non-remission were at higher risk of suicide attempt during the follow-up, strengthening the necessity of targeting specific dimensions associated with suicidal risk in these patients.

In patients who changed antidepressant at inclusion and without depression remission at week 6, thus evolving to TRD, the only factor strongly associated with depression non-remission was smaller



**Fig. 3B.** Mediation analysis for patients with treatment change (LUEUR cohort). For each effect, values are the log odds. Significant effects ( $p < 0.05$ ) are marked with \*; for the indirect effects, the significance was tested with a 95 % percentile confidence interval and the bootstrap method (5000 samples).

improvement of anxiety at week 2. In the LUEUR cohort, smaller improvement of hopelessness and SI at week 2 also were associated with depression non-remission. Our results suggest a strong link between suicidality, TRD and anxiety, as previously reported. Indeed, most studies found that patients with anxious depression are at higher risk of SI and suicide attempt (De La Vega et al., 2018; Fava et al., 2006; Ionescu et al., 2013) and of TRD (Daly et al., 2021; Souery et al., 2007). Antidepressants may not be sufficient to treat depression in patients with high anxiety levels (Ionescu et al., 2014). Moreover, in a recent meta-analysis, absence of early decrease in depression severity (depression score decrease of  $<20\%$  at week 2) was not a good predictor of depression non-remission (Olgati et al., 2018). Altogether these previous data and our present results highlight the need to target not only depression but also anxiety to achieve depression remission in suicidal patients. According to our results, non-early improvement of anxiety in depressed patients with current SI might be a better predictor of depression non-remission than non-early improvement of depression. Thus, it is crucial to target anxiety with specific drugs and/or psychotherapy (e.g. cognitive behavioral therapy) in depressed patients with current SI (Apolinário-Hagen et al., 2020; Hofmann and Gómez, 2017).

In addition, SI should be specifically targeted in suicidal patients. Indeed, in the LUEUR cohort, non-early improvement of SI was strongly associated with depression non-remission. Moreover, the mediation analysis demonstrated a strong SI mediation on depression severity at baseline and depression remission in patients who started treatment. This reinforces the hypothesis that depression with current SI could lead to TRD because depression severity at baseline alone did not explain depression remission but only through baseline SI. Although this result was not observed in the group who changed treatment, depression severity at baseline alone or through SI did not explain depression remission at week 6, suggesting the implications of other dimensions in depression non-remission. More studies are needed. However, SI seems to play a significant role in depression non-remission, especially in patients who started treatment. Moreover, many studies suggest that antidepressants are not sufficient to reduce SI (Lopez-Castroman et al., 2016; Bénédicte Nobile et al., 2021; Rihmer and Gonda, 2013) and that specific anti-suicidal medications are needed (Courtet et al., 2020), such as ketamine and esketamine that rapidly reduce SI (Abbar et al., 2022; Canuso et al., 2018). Thus, reducing SI in depressed patients with current SI might increase the possibility of depression remission, which is contrary to the general opinion. Indeed, most clinicians think that by reducing depression they will decrease SI and suicidal risk. However, different studies and our present results suggest that in suicidal patients, it may be better to target SI to reduce depression. Surprisingly, the risk of suicide attempt during the follow-up was similar in patients with and without depression remission. This may be linked to the severity of the current MDE. Indeed, some recent studies suggest that the risk of suicide

attempt is higher in patients with low/moderate depression than in patients with severe depression (McManama O'Brien et al., 2014; Rogers et al., 2018). As the sample was composed of patients who changed antidepressant at inclusion, we could hypothesize that depression was more severe (e.g. longer duration of the current episode) in these patients than in patients with first antidepressant at inclusion.

In view of these elements, depression with current SI can be seen as “difficult to treat depression”, a recent concept proposed by a consensus of experts and defined as “depression that continues to cause significant burden despite usual treatment efforts” (McAllister-Williams et al., 2020). This significant burden can be due to difficulties to achieve remission or response, as seen in depression with current SI. These experts proposed a model to manage difficult to treat depression that is applicable also to depression with current SI. The first step is to optimally control the different symptoms. Then, it is important to target the symptoms associated with bad outcomes (e.g. suicidal risk, anxiety), the symptoms that can affect quality of life and functioning (e.g. suicidal risk, sleep disturbances) and comorbidities to reduce the global symptom burden. The last step is to optimize the long-term response with an adequate prophylaxis (McAllister-Williams et al., 2020). This model is in line with the concept of precision psychiatry towards which psychiatry is moving (Salagre and Vieta, 2021). This concept refers to a new approach to mental disorders with the goal of developing psychopharmacological treatments by taking into account the patients' genetic, environmental and lifestyle variability. Indeed, considering the multiple symptoms of a MDE (e.g. anxiety, SI, hopelessness) instead of only depression, choosing adapted and efficient therapies, and assessing adequately the response to treatment (changes in the severity of different symptoms) according to the patient's profile could be the first step towards the development of precision psychiatry. Finally, SI is often associated with relational issues and a lack of support, highlighting the need for a better understanding of the patient's psychopathology and the importance of incorporating personalized psychotherapy as an adjunctive therapy (Pompili, 2024).

Our study has some limitations. First, the lack of studies on risk factors of TRD in depressed patients with current SI did not allow us to compare our results or to put them in perspective with other studies. However, this limitation highlights the fact that studies of this kind are necessary, particularly because many depressed patients have SI. Second, the limited number of suicide attempts during the follow-up in the GENESE cohort did not allow comparing the suicidal risk in the patient groups. Six weeks of follow-up may be a short period, particularly for patients over 50. Nevertheless, 4 weeks is generally sufficient to assess treatment response in most cases, and it is essential to identify non-responders early to address risk factors for non-response in the short term. Our study has also some strengths. First, even if the heterogeneity of the two cohorts preventing us from performing a pooled analysis

could be seen as a limit, the fact that results were quite similar in both cohorts finally strengthen our results. Indeed, we performed the same analyses in two independent large cohorts of >2000 outpatients with unipolar depression and found quite similar results, thus reinforcing our conclusions. Except for some sociodemographic characteristics, most of the risk factors of depression non-remission were identified in both cohorts. Differences between cohorts could be explained by differences in inclusion/exclusion criteria (*i.e.* no patient with alcohol use disorder in the GENESE cohort). Second, the use of different scales to assess different dimensions of depressive symptomatology at inclusion and at different time points during the follow-up allowed us to analyze the association between early decrease in these dimensions at week 2 and depression non-remission. Finally, this study was the first to assess risk factors of depression non-remission and TRD in depressed patients with current SI by including the early decrease of different symptoms.

To conclude, it seems that in depressed patients with current SI, non-early decrease of depression and other dimensions, such as SI, hopelessness, impulsivity, and anxiety, is the most important risk factor of depression non-remission. Moreover, non-early improvement of anxiety seems to be one of the most important risk factors of TRD in these patients. Clinicians should systematically target with specific pharmacological and non-pharmacological treatments these dimensions according to the patient's profile and also assess their changes in the short term, especially anxiety, to increase the chance of depression remission in depressed patients with current SI.

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## Data availability statement

Due to ethical and legal restrictions, data involving clinical participants cannot be made publicly available.

## CRedit authorship contribution statement

**Bénédict Nobile:** Writing – original draft, Conceptualization. **Elia Gourguechon-Buot:** Methodology, Formal analysis. **Manon Malestroit:** Methodology, Formal analysis. **Emilie Olié:** Writing – review & editing. **Emmanuel Haffen:** Writing – review & editing. **Philip Gorwood:** Writing – review & editing, Project administration. **Philippe Courtet:** Writing – review & editing, Project administration, Conceptualization.

## Declaration of competing interest

None of the authors declare conflict of interests related to this manuscript.

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## References

- Abbar, M., Demattei, C., El-Hage, W., Llorca, P.-M., Samalin, L., Demaricourt, P., Jollant, F., 2022. Ketamine for the acute treatment of severe suicidal ideation : double blind, randomised placebo controlled trial. *BMJ*, e067194. <https://doi.org/10.1136/bmj-2021-067194>.
- Alcázar-Córcoles, M.Á., Verdejo, A.J., Bouso-Sáiz, J.C., 2015. Psychometric properties of Plutchik's impulsivity scale in juvenile Spanish speaking population. *Actas Esp. Psiquiatr.* 43 (5), 161-169.
- Apolinário-Hagen, J., Drüge, M., Fritsche, L., 2020. Cognitive behavioral therapy, mindfulness-based cognitive therapy and acceptance commitment therapy for anxiety disorders : integrating traditional with digital treatment approaches. *Adv. Exp. Med. Biol.* 1191, 291-329. [https://doi.org/10.1007/978-981-32-9705-0\\_17](https://doi.org/10.1007/978-981-32-9705-0_17).
- Arias-de la Torre, J., Vilagut, G., Ronaldson, A., Serrano-Blanco, A., Martín, V., Peters, M., Alonso, J., 2021. Prevalence and variability of current depressive disorder in 27 European countries : a population-based study. *Lancet Publ. Health* 6 (10), e729-e738. [https://doi.org/10.1016/S2468-2667\(21\)00047-5](https://doi.org/10.1016/S2468-2667(21)00047-5).
- Balestri, M., Calati, R., Souery, D., Kautzky, A., Kasper, S., Montgomery, S., Serretti, A., 2016. Socio-demographic and clinical predictors of treatment resistant depression : a prospective European multicenter study. *J. Affect. Disord.* 189, 224-232. <https://doi.org/10.1016/j.jad.2015.09.033>.
- Ballard, E.D., Snider, S.L., Nugent, A.C., Luckenbaugh, D.A., Park, L., Zarate, C.A., 2017. Active suicidal ideation during clinical antidepressant trials. *Psychiatry Res.* 257, 303-308. <https://doi.org/10.1016/j.psychres.2017.07.065>.
- Bartova, L., Dold, M., Kautzky, A., Fabbri, C., Spies, M., Serretti, A., Kasper, S., 2019. Results of the European Group for the study of resistant depression (GSRD)—basis for further research and clinical practice. *World J. Biol. Psychiatry* 20 (6), 427-448. <https://doi.org/10.1080/15622975.2019.1635270>.
- Batterham, P.J., Spijker, B.A.J., Mackinnon, A.J., Cleave, A.L., Wong, Q., Christensen, H., 2019. Consistency of trajectories of suicidal ideation and depression symptoms : evidence from a randomized controlled trial. *Depress. Anxiety* 36 (4), 321-329. <https://doi.org/10.1002/da.22863>.
- Bennabi, D., Aouizerate, B., El-Hage, W., Doumy, O., Moliere, F., Courtet, P., Haffen, E., 2015. Risk factors for treatment resistance in unipolar depression : a systematic review. *J. Affect. Disord.* 171, 137-141. <https://doi.org/10.1016/j.jad.2014.09.020>.
- Bennabi, D., Charpeaud, T., Yrondi, A., Genty, J.-B., Destouches, S., Lancrenon, S., Haffen, E., 2019. Clinical guidelines for the management of treatment-resistant depression : french recommendations from experts, the French Association for Biological Psychiatry and Neuropsychopharmacology and the Fondation FondaMental. *BMC Psychiatry* 19 (1), 262. <https://doi.org/10.1186/s12888-019-2237-x>.
- Bergfeld, I.O., Mantione, M., Figuee, M., Schuurman, P.R., Lok, A., Denys, D., 2018. Treatment-resistant depression and suicidality. *J. Affect. Disord.* 235, 362-367. <https://doi.org/10.1016/j.jad.2018.04.016>.
- Bernert, R.A., Luckenbaugh, D.A., Duncan, W.C., Iwata, N.G., Ballard, E.D., Zarate, C.A., 2017. Sleep architecture parameters as a putative biomarker of suicidal ideation in treatment-resistant depression. *J. Affect. Disord.* 208, 309-315. <https://doi.org/10.1016/j.jad.2016.08.050>.
- Bjelland, I., Dahl, A.A., Haug, T.T., Neckelmann, D., 2002. The validity of the hospital anxiety and depression scale. *J. Psychosom. Res.* 52 (2), 69-77. [https://doi.org/10.1016/S0022-3999\(01\)00296-3](https://doi.org/10.1016/S0022-3999(01)00296-3).
- Canuso, C.M., Singh, J.B., Fedgchin, M., Alphas, L., Lane, R., Lim, P., Drevets, W.C., 2018. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide : results of a double-blind, randomized, placebo-controlled study. *Am. J. Psychiatry* 175 (7), 620-630. <https://doi.org/10.1176/appi.ajp.2018.17060720>.
- Coryell, W., Wilcox, H., Evans, S.J., Pandey, G.N., Jones-Brando, L., Dickerson, F., Yolken, R., 2018. Aggression, impulsivity and inflammatory markers as risk factors for suicidal behavior. *J. Psychiatr. Res.* 106, 38-42. <https://doi.org/10.1016/j.jpsychires.2018.09.004>.
- Courtet, P., Lopez-Castroman, J., Jaussent, I., Gorwood, P.A.P.M., 2014. Antidepressant dosage and suicidal ideation. *JAMA Intern. Med.* 174 (11), 1863-1865. <https://doi.org/10.1001/jamainternmed.2014.4509>.
- Courtet, P., Nobile, B., Guillaume, S., Olié, E., 2020. An urgent need for rapid anti-suicidal drugs. *French J. Psychiatry* 1, 1-4. <https://doi.org/10.1016/j.fjpsy.2020.02.003>.
- Czyz, E.K., Horwitz, A.G., King, C.A., 2016. Self-rated expectations of suicidal behavior predict future suicide attempts among adolescent and young adult psychiatric emergency patients. *Depress. Anxiety* 33 (6), 512-519. <https://doi.org/10.1002/da.22514>.
- Daly, E.J., Turkoz, I., Salvatore, G., Fedgchin, M., Ionescu, D.F., Starr, H.L., Singh, J.B., 2021. The effect of esketamine in patients with treatment-resistant depression with and without comorbid anxiety symptoms or disorder. *Depress. Anxiety* 38 (11), 1120-1130. <https://doi.org/10.1002/da.23193>.
- De La Vega, D., Giner, L., Courtet, P., 2018. Suicidality in subjects with anxiety or obsessive-compulsive and related disorders : recent advances. *Curr. Psychiatry Rep.* 20 (4), 26. <https://doi.org/10.1007/s11920-018-0885-z>.
- Demyttenaere, K., Verhaeghen, A., Dantchev, N., Grassi, L., Montejo, A.L., Perahia, D.G.S., Bauer, M., 2009. « Caseness » for depression and anxiety in a depressed outpatient population : symptomatic outcome as a function of baseline diagnostic categories. *Prim. Care Companion J. Clin. Psychiatry* 11 (6), 307-315. <https://doi.org/10.4088/PCC.08m00748blu>.
- Desseilles, M., Perroud, N., Guillaume, S., Jaussent, I., Genty, C., Malafosse, A., Courtet, P., 2012. Is it valid to measure suicidal ideation by depression rating scales? *J. Affect. Disord.* 136 (3), 398-404. <https://doi.org/10.1016/j.jad.2011.11.013>.
- Dold, M., Bartova, L., Fugger, G., Kautzky, A., Souery, D., Mendlewicz, J., Kasper, S., 2018. Major depression and the degree of suicidality : results of the European group for the study of resistant depression (GSRD). *Int. J. Neuropsychopharmacol.* 21 (6), 539-549. <https://doi.org/10.1093/ijnp/pyy009>.
- EMA. (2013). *Guideline on clinical investigation of medicinal products in the treatment of depression*.
- Fava, M., Rush, A.J., Alpert, J.E., Carmin, C.N., Balasubramani, G., Wisniewski, S.R., Shores-Wilson, K., 2006. What clinical and symptom features and comorbid disorders characterize outpatients with anxious major depressive disorder : a replication and extension. *Can. J. Psychiatry* 51 (13), 823-835. <https://doi.org/10.1177/070674370605101304>.
- Friedman, S., Samuelian, J.-C., Lancrenon, S., Even, C., Chiarelli, P., 2001. Three-dimensional structure of the hospital anxiety and depression scale in a large french primary care population suffering from major depression. *Psychiatry Res.* 104 (3), 247-257. [https://doi.org/10.1016/S0165-1781\(01\)00309-2](https://doi.org/10.1016/S0165-1781(01)00309-2).



- Gronemann, F.H., Jørgensen, M.B., Nordentoft, M., Andersen, P.K., Osler, M., 2021. Treatment-resistant depression and risk of all-cause mortality and suicidality in Danish patients with major depression. *J. Psychiatr. Res.* 135, 197–202. <https://doi.org/10.1016/j.jpsychires.2021.01.014>.
- Gusmão, R., Quintão, S., McDaid, D., Arensman, E., Van Audenhove, C., Coffey, C., Hegerl, U., 2013. Antidepressant utilization and suicide in Europe : an ecological multi-national study. *PLoS ONE* 8 (6), e66455. <https://doi.org/10.1371/journal.pone.0066455>.
- Hofmann, S.G., Gómez, A.F., 2017. Mindfulness-based interventions for anxiety and depression. *Psychiatr. Clin. North Am.* 40 (4), 739–749. <https://doi.org/10.1016/j.psc.2017.08.008>.
- Ionescu, D.F., Niciu, M.J., Henter, I.D., Zarate, C.A., 2013. Defining anxious depression : a review of the literature. *CNS Spectr.* 18 (5), 252–260. <https://doi.org/10.1017/S1092852913000114>.
- Ionescu, D.F., Niciu, M.J., Richards, E.M., Zarate, C.A., 2014. Pharmacologic treatment of dimensional anxious depression : a review. *Prim. Care Companion CNS Disord.* <https://doi.org/10.4088/PCC.13r01621>.
- Kautzky, A., Dold, M., Bartova, L., Spies, M., Kranz, G.S., Souery, D., Kasper, S., 2019. Clinical factors predicting treatment resistant depression : affirmative results from the European multicenter study. *Acta Psychiatr. Scand.* 139 (1), 78–88. <https://doi.org/10.1111/acps.12959>.
- Kim, J., Farchione, T., Potter, A., Chen, Q., Temple, R., 2019. Esketamine for treatment-resistant depression—first FDA-approved antidepressant in a new class. *New Engl. J. Med.* 381 (1), 1–4. <https://doi.org/10.1056/NEJMp1903305>.
- Kliem, S., Lohmann, A., Mölle, T., Brähler, E., 2018. Psychometric properties and measurement invariance of the Beck hopelessness scale (BHS) : results from a German representative population sample. *BMC Psychiatry* 18 (1), 110. <https://doi.org/10.1186/s12888-018-1646-6>.
- Lopez-Castroman, J., Jaussent, I., Gorwood, P., Courtet, P., 2016. Suicidal depressed patients respond less well to antidepressants in the short term. *Depress. Anxiety* 33 (6), 483–494. <https://doi.org/10.1002/da.22473>.
- Lopez-Castroman, J., Jaussent, I., Gorwood, P., Courtet, P., 2020. Activation syndrome induced by the antidepressant tianeptine and suicidal ideation : evidence from a large depressed outpatient sample. *Progr. Neuro-Psychopharmacol. Biol. Psychiatry* 97, 109762. <https://doi.org/10.1016/j.pnpbp.2019.109762>.
- McAllister-Williams, R.H., Arango, C., Blier, P., Demyttenaere, K., Falkai, P., Gorwood, P., Rush, A.J., 2020. The identification, assessment and management of difficult-to-treat depression : an international consensus statement. *J. Affect. Disord.* 267, 264–282. <https://doi.org/10.1016/j.jad.2020.02.023>.
- McManama O'Brien, K.H., Becker, S.J., Spirito, A., Simon, V., Prinstein, M.J., 2014. Differentiating adolescent suicide attempters from ideators : examining the interaction between depression severity and alcohol use. *Suicide Life-Threaten. Behav.* 44 (1), 23–33. <https://doi.org/10.1111/sltb.12050>.
- Nobile, B., Jaussent, I., Gorwood, P., Lopez Castroman, J., Olié, E., Guillaume, S., Courtet, P., 2018. Tianeptine is associated with lower risk of suicidal ideation worsening during the first weeks of treatment onset compared with other antidepressants : a naturalistic study. *J. Psychiatr. Res.* 96, 167–170. <https://doi.org/10.1016/j.jpsychires.2017.10.007>.
- Nobile, B., Olié, E., Dubois, J., Benramdane, M., Guillaume, S., Courtet, P., 2022. Characterization of suicidal depression : a one-year prospective study. *Eur. Psychiatry* 2022.16. <https://doi.org/10.1192/j.eurpsy.2022.16>.
- Nobile, Bénédicte, Belzeaux, R., Aouizerate, B., Dubertret, C., Haffen, E., Llorca, P.-M., Olié, E., 2023. Clinical characteristics associated with discrepancies between self- and clinician-rated suicidal ideation in patients with bipolar disorder (FACE-BD cohort). *Psychiatry Res.* 321, 115055. <https://doi.org/10.1016/j.psychres.2023.115055>.
- Nobile, Bénédicte, Dubois, J., Aouizerate, B., Aubin, V., Loftus, J., Bellivier, F., Olié, E., 2020. Characterization of depressed bipolar patients with current suicidal ideation. *Austr. New Zeal. J. Psychiatry*, 000486742096374. <https://doi.org/10.1177/0004867420963744>.
- Nobile, Bénédicte, Olié, E., Dubois, J., Guillaume, S., Gorwood, P., Courtet, P., 2021. Characteristics and treatment outcome of suicidal depression : two large naturalistic cohorts of depressed outpatients. *Austr. New Zeal. J. Psychiatry*, 0004867421102569. <https://doi.org/10.1177/00048674211025697>.
- Oligiati, P., Serretti, A., Souery, D., Dold, M., Kasper, S., Montgomery, S., Mendlewicz, J., 2018. Early improvement and response to antidepressant medications in adults with major depressive disorder. Meta-analysis and study of a sample with treatment-resistant depression. *J. Affect. Disord.* 227, 777–786. <https://doi.org/10.1016/j.jad.2017.11.004>.
- Orsini, L.S., O'Connor, S.J., Mohwinkel, M.T., Marwood, L., Pahwa, A.S., Bryder, M.N., Levine, S.P., 2022. Observational study to characterize treatment-resistant depression in Germany, France and the United Kingdom : analysis of real-world data collected through a survey of healthcare professionals. *Curr. Med. Res. Opin.* 38 (12), 2219–2226. <https://doi.org/10.1080/03007995.2022.2113692>.
- Pompili, M., 2024. On mental pain and suicide risk in modern psychiatry. *Ann. Gen. Psychiatry* 23 (1), 6. <https://doi.org/10.1186/s12991-024-00490-5>.
- Reeves, H., Batra, S., May, R.S., Zhang, R., Dahl, D.C., Li, X., 2008. Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder : a randomized, double-blind, placebo-controlled pilot study. *J. Clin. Psychiatry* 69 (8), 1228–1236. <https://doi.org/10.4088/JCP.v69n0805>.
- Ribeiro, J.D., Huang, X., Fox, K.R., Franklin, J.C., 2018. Depression and hopelessness as risk factors for suicide ideation, attempts and death : meta-analysis of longitudinal studies. *Brit. J. Psychiatry* 212 (5), 279–286. <https://doi.org/10.1192/bjp.2018.27>.
- Rihmer, Z., Gonda, X., 2013. Pharmacological prevention of suicide in patients with major mood disorders. *Neurosci. Biobehav. Rev.* 37 (10), 2398–2403. <https://doi.org/10.1016/j.neubiorev.2012.09.009>.
- Rogers, M.L., Ringer, F.B., Joiner, T.E., 2018. The association between suicidal ideation and lifetime suicide attempts is strongest at low levels of depression. *Psychiatry Res.* 270, 324–328. <https://doi.org/10.1016/j.psychres.2018.09.061>.
- Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Fava, M., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps : a STAR\*D report. *Am. J. Psychiatry* 163 (11), 1905–1917. <https://doi.org/10.1176/ajp.2006.163.11.1905>.
- Salagre, E., Vieta, E., 2021. Precision psychiatry : complex problems require complex solutions. *Eur. Neuropsychopharmacol.* 52, 94–95. <https://doi.org/10.1016/j.euroneuro.2021.07.003>.
- Smith, K.A., Cipriani, A., 2017. Lithium and suicide in mood disorders : updated meta-review of the scientific literature. *Bipolar Disord.* 19 (7), 575–586. <https://doi.org/10.1111/bdi.12543>.
- Souery, D., Oswald, P., Massat, I., Bailer, U., Bollen, J., Demyttenaere, K., 2007. Clinical factors associated with treatment resistance in major depressive disorder : results from a European multicenter study. *J. Clin. Psychiatry* 68 (07), 1062–1070. <https://doi.org/10.4088/JCP.v68n0713>.
- The Measurement of Emotions—1st Edition. (s. d.). Consulté 19 avril 2019, à l'adresse <https://www.elsevier.com/books/the-measurement-of-emotions/plutchik/978-0-12-558704-4>.
- Uhl, E., Raybin, H.B., Liu, N.H., Garza, M., Barakat, S., Muñoz, R.F., Leykin, Y., 2023. Discrepancies in suicide screenings : results from an international study. *J. Affect. Disord.* 320, 18–21. <https://doi.org/10.1016/j.jad.2022.09.122>.
- van Ballegooijen, W., Eikelenboom, M., Fokkema, M., Riper, H., van Hemert, A.M., Kerkhof, A.J.F.M., Smit, J.H., 2019. Comparing factor structures of depressed patients with and without suicidal ideation, a measurement invariance analysis. *J. Affect. Disord.* 245, 180–187. <https://doi.org/10.1016/j.jad.2018.10.108>.
- Voegeli, G., Ramoz, N., Shekhtman, T., Courtet, P., Gorwood, P., Kelsø, J.R., 2016. Neurotrophin genes and antidepressant-worsening suicidal ideation : a prospective case-control study. *Int. J. Neuropsychopharmacol.* (11), 19. <https://doi.org/10.1093/ijnp/pyw059>.
- Wagner, S., Engel, A., Engelmann, J., Herzog, D., Dreimüller, N., Müller, M.B., Lieb, K., 2017. Early improvement as a resilience signal predicting later remission to antidepressant treatment in patients with Major Depressive Disorder : systematic review and meta-analysis. *J. Psychiatr. Res.* 94, 96–106. <https://doi.org/10.1016/j.jpsychires.2017.07.003>.
- Wang, S.-M., Kim, N.-Y., Na, H.-R., Lim, H.K., Woo, Y.S., Pae, C.-U., Bahk, W.-M., 2021. Rapid onset of intranasal Esketamine in patients with treatment resistant depression and major depression with suicide ideation : a meta-analysis. *Clin. Psychopharmacol. Neurosci.* 19 (2), 341–354. <https://doi.org/10.9758/cpn.2021.19.2.341>.
- World Health Organization. (2017). *Depression and other common mental disorders : global health estimates*. Consulté à l'adresse <https://apps.who.int/iris/handle/10665/254610>.
- Yrondi, A., Javelot, H., Nobile, B., Boudieu, L., Aouizerate, B., Llorca, P.-M., Samalin, L., 2024. French society for biological psychiatry and neuropsychopharmacology (AFPBN) guidelines for the management of patients with partially responsive depression and treatment-resistant depression : update 2024. *L'Encephale*. <https://doi.org/10.1016/j.encep.2023.11.029>. S0013-7006(24)00019-8.
- Zanardi, R., Carminati, M., Attanasio, F., Fazio, V., Maccario, M., Colombo, C., 2024. How different definition criteria may predict clinical outcome in treatment resistant depression : results from a prospective real-world study. *Psychiatry Res.* 334, 115818. <https://doi.org/10.1016/j.psychres.2024.115818>.
- Zhou, X., Keitner, G.I., Qin, B., Ravindran, A.V., Bauer, M., Del Giovane, C., Xie, P., 2015. Atypical antipsychotic augmentation for treatment-resistant depression : a systematic review and network meta-analysis. *Int. J. Neuropsychopharmacol.* 18 (11), pyv060. <https://doi.org/10.1093/ijnp/pyv060>.
- Zisook, S., Trivedi, M.H., Warden, D., Lebowitz, B., Thase, M.E., Stewart, J.W., Rush, A. J., 2009. Clinical correlates of the worsening or emergence of suicidal ideation during SSRI treatment of depression : an examination of citalopram in the STAR\*D study. *J. Affect. Disord.* 117 (1–2), 63–73. <https://doi.org/10.1016/j.jad.2009.01.002>.