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Research paper

Early effects predict trajectories of response to esketamine in treatment-resistant depression

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ABSTRACT

Background: The efficacy of esketamine in treatment-resistant depression (TRD) has been confirmed. However, its administration is expensive and restrictive, with limited knowledge on how long the treatment should be continued. Predicting the treatment outcome would benefit patients and alleviate the global treatment cost. We aimed to define distinct trajectories of treatment response and assess their predictability.
Methods: In this longitudinal study, two independent samples of patients with unipolar or bipolar TRD were treated with esketamine in real-world settings. Depression severity was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) before each esketamine administration. Latent class analyses were used to define trajectories of response.
Results: In the original sample ($N = 50$), we identified two classes whose trajectories depicted response and non-response, respectively. The model was validated in the confirmatory sample ($N = 55$). Class membership was influenced by a few baseline characteristics such as concomitant benzodiazepine medication, number of depressive episodes or polarity. On the other hand, after only two esketamine administrations, the MADRS score predicted the 90-day trajectory of response with an accuracy of 80 %.
Limitations: This observational study is not placebo-controlled. Therefore, its results and their generalizability need to be confirmed in experimental settings.
Conclusions: After the first administrations of esketamine, the MADRS score has a good capacity to predict the most plausible trajectory of response. While thresholds and their predictive values need to be confirmed, this finding suggests that clinicians could base on MADRS scores their decision to discontinue treatment because of poor remaining chances of treatment response.

1. Introduction

Depression is highly prevalent, affecting about 5 % of adults worldwide (World Health Organization, 2021). It is a leading cause of disability (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018), impairing physical, mental, social and work functioning, and decreasing quality of life (Hohls et al., 2021; Jaffe et al., 2019). It significantly increases odds of suicidal ideation, attempt and

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death (Ribeiro et al., 2018). Depression is also associated with a significant economic burden due to the increased use of healthcare resources (Jaffe et al., 2019).

After a first line of treatment, the remission rate in unipolar depression is as low as 37 % (Rush et al., 2006). After four lines of treatment, a third of patients still do not achieve remission (Rush et al., 2006). In bipolar depression, the remission rate is also low with standard treatments, e.g. around 50 % with quetiapine (Suppes et al., 2010). Although there is no consensus definition, treatment-resistant depression (TRD) is most commonly defined as a depression with a minimum of two prior treatment failures despite adequate dose, duration and observance (Fountoulakis et al., 2020; Gaynes et al., 2020).

Ketamine is a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist. It has been used as a dissociative anesthetic since the 1960s (Anis et al., 1983). More recently, its rapid antidepressant effects were brought to light (Berman et al., 2000). A single administration of ketamine can alleviate symptoms of depression within four hours and its antidepressant effects last up to seven days (McGirr et al., 2015; Riggs and Gould, 2021). Esketamine, the S-enantiomer of ketamine, is a more potent NMDA receptor antagonist and has higher analgesic potency than its enantiomer R-ketamine (Swainson et al., 2019). In 2019, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved esketamine, in conjunction with an oral antidepressant, for the treatment of TRD (European Medicines Agency (EMA), 2019; Food and Drug Administration (FDA), 2019).

Recent meta-analyses have confirmed the efficacy of adjunctive intranasal esketamine for treating unipolar depression that has failed to respond to two or more antidepressants (Bahji et al., 2022; Dold et al., 2020; Papakostas et al., 2020). However, since it is a dissociative hallucinogen drug, its use is strictly regulated. Esketamine can only be administered in a hospital setting. Besides, due to potential side effects such as hypertension or dissociation, each administration requires a two-hour monitoring. These requirements limit the access to esketamine. Another challenge is its cost, as the annual cost for the first year of treatment is estimated at $36,500 (Bozymski et al., 2020). Nevertheless, a study of its cost-per-remitter found that esketamine is a cost-effective treatment option for TRD (Desai et al., 2021). Considering this full picture, being able to quickly identify potential responders would both benefit the patients and alleviate the costs.

While traditional statistical analyses assume homogeneity of the treatment response across the clinical population, latent class analyses consider that not all patients equally benefit from treatment (Maalouf et al., 2012). These analyses have been used to identify subgroups of patients treated for depression characterized by distinct trajectories of response (Maalouf et al., 2012; Larsen et al., 2020; Rhebergen et al., 2015; Goerigk et al., 2021; Uher et al., 2011; Gueorguieva et al., 2011; Kelley et al., 2018). Identifying classes and predictive factors of membership in these classes can provide valuable information on expectable courses of treatment response (Maalouf et al., 2012).

Since patients respond to treatment differentially, and given that the administration of esketamine comes with constraints (i.e. administration restricted to hospital settings, two-hour monitoring, and elevated costs), we aimed to examine the trajectories of response to esketamine and identify indicators that can predict whether a patient is likely to respond or not. To do so, we conducted a longitudinal study in two independent real-life samples of adult patients treated with esketamine for TRD. More specifically, we measured before each esketamine administration the Montgomery-Åsberg Depression Rating Scale (MADRS) score, a 10-item scale commonly used to assess responses to antidepressant treatments (Montgomery and Asberg, 1979). The first objective was to delineate in the first sample, with a longitudinal latent class analysis, homogeneous groups of patients based on their trajectories of response to esketamine. We hypothesized that a limited number of trajectories would distinguish between responders and non-responders, and that the results could be replicated in the second sample. The second objective of this study was to identify baseline factors and a time point predicting the trajectory of response, so that patients who are unlikely to respond can discontinue the treatment as quickly as possible in order to start another intervention with a higher chance of success. The hypothesis was that the most likely trajectory of response could be predicted from some baseline factors or from the early effects (or absence thereof) observed after a certain number of esketamine administrations.

2. Methods

The protocol was submitted to an ethic committee (CLEP, Paris) and was considered as conform to research ethical standards (decision AAA-2022-08043). All patients received detailed information on the protocol and signed an informed consent to participate.

2.1. Participants

2.1.1. Original sample

Longitudinal data were collected from adult inpatients or outpatients (age $\geq$ 18 years) treated with esketamine for unipolar or bipolar TRD at the *Clinique des Maladies Mentales et de l'Encéphale*, a university department of a general hospital (GHU Paris) in Paris, from October 2019 to February 2022.

Patients were included in this study if they fulfilled the following criteria: 1) diagnosis of TRD, 2) a MADRS score at baseline higher than or equal to 25, 3) age over 18 years, 4) prescription of intranasal esketamine according to the standard treatment scheme.

Exclusion criteria included previous treatment with IV ketamine in the three months prior to intranasal esketamine treatment, receiving less than three administrations of esketamine, and concomitant schizophrenia spectrum disorder.

2.1.2. Confirmatory sample

For the confirmatory study, longitudinal data were collected from an independent cohort of patients treated at the *Pôle Hospitalo-Universitaire Psychiatrie Paris 15*, an independent university department of the same general hospital (GHU Paris) in Paris, from October 2019 to December 2021. The same inclusion and exclusion criteria as described above were applied.

2.2. Procedure

2.2.1. Data collection and variables

Electronic medical records were reviewed and, for all included patients, demographic, clinical and esketamine treatment data were collected. Collected data included: sociodemographic data (gender, age, employment status, and marital status); clinical data, including psychiatric comorbidities (history of suicide attempt, personality disorder, smoking, alcohol use disorder or other substance use disorder) and family history of alcohol use disorder or major depressive episode; somatic comorbidities including endocrinological, neurological and cardiological pathologies, sleep apnea syndrome, dyslipidemia, and stroke; disorder characteristics (unipolar or bipolar, lifetime duration of depression, number of episodes over life, lifetime electroconvulsive therapy -ECT- trial); characteristics of the current episode (duration, Maudsley staging method duration score, total Maudsley score, concomitant antidepressant treatment, associated suicidal ideation, ECT trial on the episode); characteristics of the esketamine treatment (administration dates, initial dosage, any dosage changes during treatment, side effects, and the MADRS score at each administration).

The MADRS is a scale built to be sensitive to change in patients treated with antidepressants (Montgomery et al., 1985). It consists of ten items that address the psychological symptoms of depression, namely apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts (Montgomery and Asberg,

1979). Each item is rated on a scale ranging from 0 to 6. The MADRS score therefore ranges from 0 to 60, with higher scores indicating more severe depression (Lam et al., 2006). While there is no consensus on cut-off scores (Rozjabek et al., 2022), we defined remission as a MADRS total score $\leq$ 12 like other esketamine trials (Fedgchin et al., 2019; Popova et al., 2019).

The Maudsley staging method is a multidimensional tool incorporating three factors: treatment resistance, symptom severity, and duration of the current episode (Fekadu et al., 2009). Duration of the current episode is classified into three categories: acute (less than a year), subacute (between one and two years), and chronic (more than two years). The total Maudsley score indicates the illness severity: mild for a score ranging from 3 to 6, moderate for a score ranging from 7 to 10, and severe for a score ranging from 11 to 15 (Fekadu et al., 2018).

2.2.2. Esketamine treatment

The treatment was administered in two phases according to the standard schedule and dosage (European Medicines Agency (EMA), 2019). During the induction phase (IND), patients were administered esketamine (from 28 to 56 mg at first administration, then 56 or 84 mg) twice a week for four weeks. During the optimization/maintenance phase (OPT/MAINT), one dose (56 or 84 mg) per week was administered for four weeks, followed by one dose (56 or 84 mg) every fortnight, if possible for four months. Since treatments were administered in a real-life, unconstrained setting, the scheme could be adjusted based on clinicians' decisions or patients' constraints. Before each esketamine administration, patients systematically received a psychiatric examination including a MADRS assessment.

2.2.3. Outcomes

MADRS scores were measured by a trained psychiatrist before each esketamine administration.

Response to treatment was assessed at the eighth administration (at approximately 28 days). Remission was defined as a MADRS total score $\leq$ 12. A reduction of the MADRS total score of >50 % from baseline indicated response to treatment (Fedgchin et al., 2019; Popova et al., 2019).

2.3. Statistical analysis

2.3.1. Latent class analysis

To identify homogeneous groups of patients according to their longitudinal trajectories of response to esketamine treatment, i.e. the evolution of MADRS scores, we built a latent class mixed model (LCMM) (Proust-Lima et al., 2017, 2013) using the *lcmm* package (version 1.9.5) for R studio (Proust-Lima et al., 2017). The models were compared using Bayesian Information Criteria (BIC), entropy and class size. Model fit was measured using the average posterior probability of assignments (Lennon et al., 2018). For more details, see Supplementary Information.

The analysis was performed on the data from the original sample, separately on the longitudinal data of the IND phase (over 30 days) and the total data (IND + OPT/MAINT phases, over 90 days). Then, as a confirmatory study analysis, the best-fitting LCMM identified for the original sample was applied to the confirmatory sample to verify its consistency and reproducibility.

The degree of association between classifications at 30 days and at 90 days was assessed with the Somers' D test.

2.3.2. Association between patients' characteristics and outcomes

Analyses were performed using SPPS v26 (released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Patients' features at baseline were compared across the whole sample depending on the latent class (Class 1 versus Class 2). Comparisons were made using the chi-square test or Fisher exact-test for categorical variables, and Student's t-test or Mann-Whitney *U* test for continuous variables. The Bonferroni correction to account for multiple comparisons was applied.

The role of significant factors was then tested in a multivariate approach (logistic regression).

2.3.3. ROC analysis

To determine the predictability of the 30-day and 90-day trajectories of response, we performed across the whole sample, for each MADRS assessment (from baseline to T6), receiver-operating characteristic (ROC) analyses with the MADRS score as the dependent variable. For each assessment, the area under the curve (AUC) was computed and the cutoff MADRS score associated with the highest Youden's index was selected (Youden, 1950). Values associated with each cutoff such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and odds ratio (OR) were then calculated (more details in Supplementary Information) (Glas et al., 2003; Tenny and Hoffman, 2022).

3. Results

3.1. Sample characteristics

The original sample initially consisted of 53 patients treated with esketamine for TRD. Among them, 50 (aged between 18 and 87, mean [SD] = 53.5 [16.4]) were eligible. The confirmatory sample, a second and independent cohort, initially included 67 patients, and 55 (aged between 21 and 91, mean [SD] = 49.8 [17.5]) were eligible (Supplementary Fig. S1). Baseline characteristics are reported in Table 1. Details on concomitant treatments are given in Table S1.

Compared to the original sample, we observed in the confirmatory sample a greater severity of disease with, in particular, a higher Maudsley score (9.3 vs 8.4; $p = 0.049$), a higher occurrence of suicidal ideation (96.4 % vs 52.0 %; $p < 0.001$), and a higher number of concomitant treatments (6.6 vs 4.6; $p = 0.007$). There was a lower occurrence of personality disorders (9.1 % vs 28.0 %; $p = 0.021$) and cardiovascular disorders (12.7 % vs 34.0 %; $p = 0.011$; Table 1).

Among the whole sample, 55 (52.4 %) were responders and 40 (38.1 %) were remitters. More specifically, 27 (54.0 %) patients from the original sample and 28 (50.9 %) from the confirmatory sample were responders, while 20 (40.0 %) and 20 (36.4 %) were remitters, respectively.

3.2. Latent class analysis

3.2.1. Original sample

In the two latent class analyses (for longitudinal data over 30 days and 90 days, respectively), the model that best fitted the cloud of individual trajectories was the two-class quadratic model adjusted for the MADRS score at baseline (Supplementary Information, Table S2).

Class 1 was characterized by a faster, greater and more stable decrease of MADRS scores than Class 2 (Fig. 1A and B).

In the 30-day model, Class 1 counted 15 (30.0 %) patients. Response and remission rates in Class 1 were 86.7 % and 73.3 %, respectively, compared to 40.0 % and 25.7 % in Class 2 (Table 2).

In the 90-day model, Class 1 counted 35 (70.0 %) patients. It included 25 (92.6 %) of the 27 responders and 20 (100.0 %) of the 20 remitters. In Class 1, response and remission rates were 71.4 % and 57.1 %, respectively, compared to 13.3 % and 0.0 % in Class 2 (Table 3).

The association between classification at 30 days and at 90 days was significant (Somers' D = 0.429; $p < 0.001$), with 20 (40.0 %) patients switching from Class 2 to Class 1 while no patient moved from Class 1 to Class 2 (Table S3).

3.2.2. Confirmatory sample

When applying the latent class model identified for the original sample to the longitudinal data of the confirmatory sample, the model met the convergence criteria in the induction phase and over the entire

Table 1
Baseline characteristics in the original and confirmatory samples.

	All patients (*N* = 105)	Original sample (*N* = 50)	Confirmatory sample (*N* = 55)	p
Demographic characteristics				
Age, mean (SD)	51.6 (17.0)	53.5 (16.4)	49.8 (17.5)	0.255
Gender, females	68 (64.8 %)	35 (70.0 %)	33 (60.0 %)	0.284
BMI, mean (SD)	24.9 (5.4)	24.5 (5.0)	25.4 (6.1)	0.523
Marital status				0.298
Single	28 (26.7 %)	10 (20.0 %)	18 (32.7 %)	
Widowed / Divorced	29 (27.6 %)	14 (28.0 %)	15 (27.3 %)	
Couple	48 (45.7 %)	26 (52.0 %)	22 (40.0 %)	
Employment status				0.317
Retired	20 (19.0 %)	11 (22.0 %)	9 (16.4 %)	
Off work or invalidity	64 (61.0 %)	32 (64.0 %)	32 (58.2 %)	
Regular	21 (20.0 %)	7 (14.0 %)	14 (25.5 %)	
Tobacco				0.174
Never	75 (71.4 %)	40 (80.0 %)	35 (63.6 %)	
Weaned	16 (15.2 %)	5 (10.0 %)	11 (20.0 %)	
Active	14 (13.3 %)	5 (10.0 %)	9 (16.4 %)	
Characteristics of the current depressive episode				
Current suicidal ideation	79 (75.2 %)	26 (52.0 %)	53 (96.4 %)	<0.001
Maudsley				0.110
Acute (≤ 12 months)	56 (53.3 %)	25 (50.0 %)	31 (56.4 %)	
Sub-Acute (12–24 months)	17 (16.2 %)	12 (24.0 %)	5 (9.1 %)	
Chronic (≥ 24 months)	32 (30.5 %)	13 (26.0 %)	19 (34.5 %)	
Maudsley Total, mean (SD)	8.8 (2.3)	8.4 (2.2)	9.3 (2.2)	0.049
No. of current treatments, mean (SD)	5.7 (3.8)	4.6 (3.3)	6.6 (4.1)	0.007
Disease features				
No. of hospitalizations, mean (SD)	3.4 (3.1)	3.4 (3.5)	3.5 (2.7)	0.255
No. of episodes, mean (SD)	4.0 (2.6)	3.9 (2.4)	4.1 (2.7)	0.769
Lifetime duration of depression				0.211
<2 years	11 (10.6 %)	4 (8.0 %)	7 (13.0 %)	
2–5 years	39 (37.5 %)	23 (46.0 %)	16 (29.6 %)	
>5 years	54 (51.9 %)	23 (46.0 %)	31 (57.4 %)	
Polarity				0.416
Unipolar	69 (65.7 %)	35 (70.0 %)	34 (61.8 %)	
Bipolar	36 (34.3 %)	15 (30.0 %)	21 (38.2 %)	
Comorbidity				
Personality disorder	19 (18.1 %)	14 (28.0 %)	5 (9.1 %)	0.021
Alcohol use disorder	14 (13.3 %)	9 (18.0 %)	5 (9.1 %)	0.252
Drug use disorder	19 (18.1 %)	11 (22.0 %)	8 (14.5 %)	0.447
Suicide attempt	49 (46.7 %)	20 (40.0 %)	29 (52.7 %)	0.241
Cardiovascular disorder	24 (22.9 %)	17 (34.0 %)	7 (12.7 %)	0.011
Neurological disorder	11 (10.5 %)	3 (6.0 %)	8 (14.5 %)	0.207
Obstructive sleep apnea	10 (9.5 %)	6 (12.0 %)	4 (7.3 %)	0.513
Endocrine disease	21 (20.0 %)	5 (10.0 %)	5 (9.1 %)	1.000
Dyslipidemia	10 (9.5 %)	10 (20.0 %)	11 (20.0 %)	1.000
Previous stroke	2 (1.9 %)	1 (2.0 %)	1 (1.8 %)	1.000
Family history				
Alcohol use disorder	10 (9.5 %)	7 (14.0 %)	3 (5.5 %)	0.187
Major depressive episodes	63 (60.0 %)	30 (60.0 %)	33 (60.0 %)	1.000
Treatment				
Antidepressants				0.002
Only one AD	61 (68.5 %)	36 (85.7 %)	25 (53.2 %)	
Two AD	22 (24.7 %)	6 (14.3 %)	16 (34.0 %)	
Three AD	6 (6.7 %)	0 (0.0 %)	6 (12.8 %)	
Lamotrigine	21 (20.0 %)	8 (16.0 %)	13 (23.6 %)	0.464
Lithium	24 (22.9 %)	4 (8.0 %)	20 (36.4 %)	<0.001
Benzodiazepine	41 (39.0 %)	25 (50.0 %)	16 (29.1 %)	0.045
Atypical antipsychotics	31 (29.5 %)	6 (12.0 %)	25 (45.5 %)	<0.001
Electroconvulsive therapy				
Lifetime	29 (27.6 %)	13 (26.0 %)	16 (29.1 %)	0.828
Current episode	18 (17.1 %)	7 (14.0 %)	11 (20.0 %)	0.449
Response				
MADRS at baseline, mean (SD)	33.4 (6.0)	32.7 (6.1)	34.0 (5.8)	0.252
MADRS at T7, mean (SD)	17.4 (10.4)	16.4 (9.6)	18.3 (11.1)	0.351
MADRS final, mean (SD)	17.9 (11.7)	18.0 (12.4)	17.7 (11.2)	0.906
Responders	55 (52.4 %)	27 (54.0 %)	28 (50.9 %)	0.845
Remitters	40 (38.1 %)	20 (40.0 %)	20 (36.4 %)	0.841

Unless "Mean (SD)" is stated, values correspond to No. (%).
p-values correspond to Student's t or Mann-Whitney *U* tests for continuous variables and chi-square or Fisher exact tests for categorical variables.
AD: antidepressant; BMI: body mass index; df: degree of freedom; MADRS: Montgomery-Asberg depression rating scale; p: *p*-value; SD: standard deviation; T7: MADRS score at the eighth assessment (after seven administrations) used to define response and remission.

treatment period (more details in Supplementary information).

In the 30-day model (Fig. 1C), Class 1 counted 28 (50.9 %) patients. Response and remission rates in Class 1 were 89.3 % and 67.9 %, respectively, compared to 11.1 % and 3.7 % in Class 2 (Table 2).

In the 90-day model (Fig. 1D), Class 1 counted 31 (56.4 %) patients. It included 25 (89.3 %) of the 28 responders and 18 (90.0 %) of the 20 remitters. In Class 1, response and remission rates were 80.6 % and 58.1 %, respectively, compared to 12.5 % and 8.3 % in Class 2 (Table 3).

The association between classes at 30 days and at 90 days was significant (Somers' D = 0.749; $p < 0.001$), with 7 (12.7 %) patients moving from a class to the other one (Table S3).

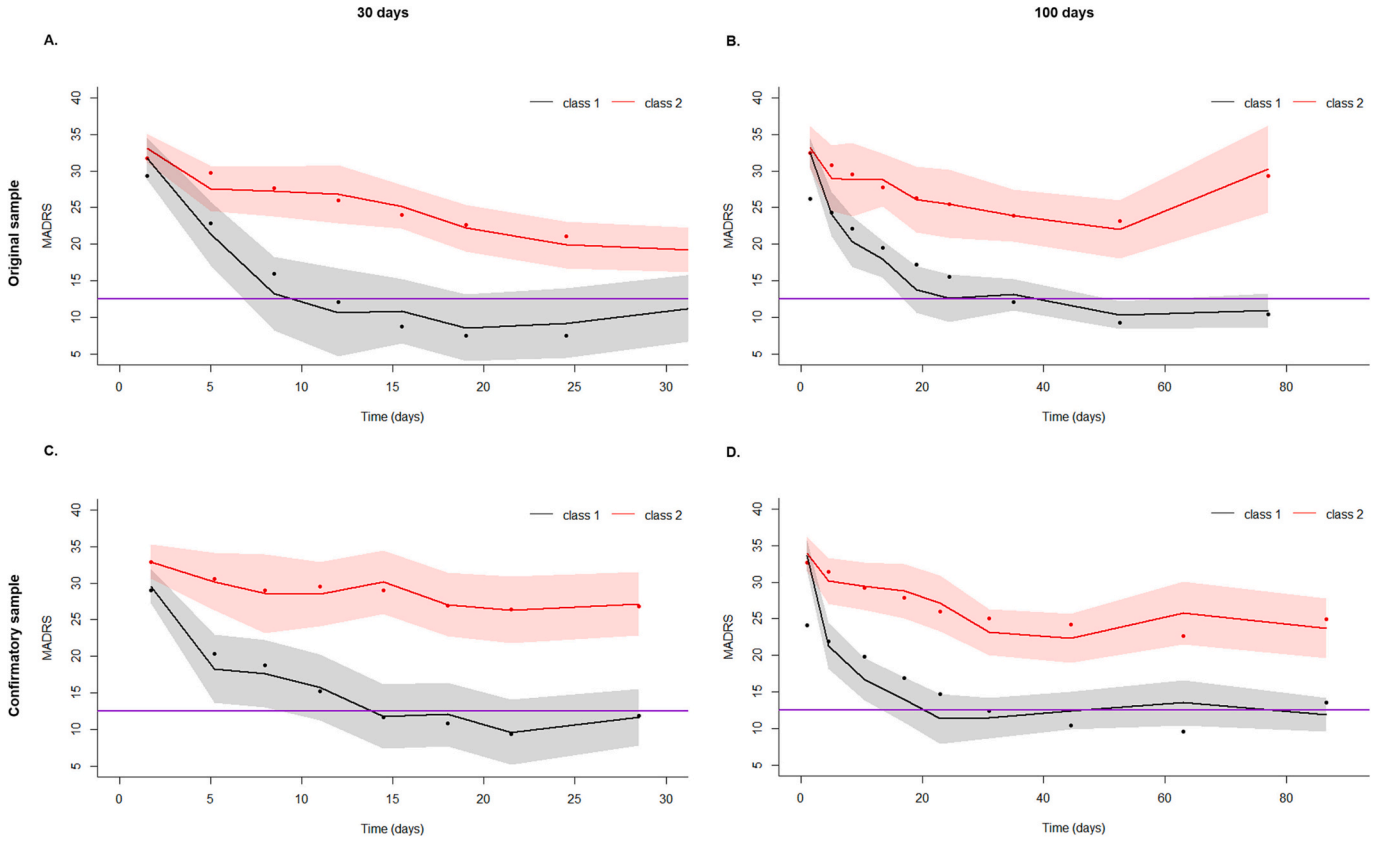

Fig. 1. Latent classes defined at the end of the induction phase (after 30 days of treatment) and at the end of the entire period of treatment (90 days). Trajectories represent the evolution of MADRS scores over time for the original sample (A and B) and the confirmatory sample (C and D). The model was the two-class quadratic model adjusted for the MADRS score at baseline. Error bars correspond to 95 % confidence intervals.

3.3. Association between patients' baseline characteristics and trajectories

In the 30-day model, across the whole sample, compared to Class 2, we observed in Class 1 more suicidal ideation ($p = 0.040$), lower Maudsley total scores ($p = 0.010$), a higher proportion of acute disease and a lower proportion of sub-acute and chronic disease according to the Maudsley staging method ($\chi^2 = 6.1$, df = 2, $p = 0.047$), a lower number of depressive episodes ($p = 0.008$). Some treatments were unevenly distributed: compared to Class 2, Class 1 included a lower proportion of patients with concomitant benzodiazepine medication ($p < 0.001$) or with a lifetime use of electroconvulsive therapy ($p = 0.014$) and a higher proportion of patients treated with lithium ($p = 0.019$). Moreover, tendencies were observed for lifetime duration of depression ($\chi^2 = 5.0$, df = 2, $p = 0.082$), number of hospitalizations ($p = 0.073$), and polarity ($p = 0.095$; Table 2).

Testing these factors using a multivariate approach with a logistic regression showed that the odds of being in Class 1 were significantly reduced by a higher number of depressive episodes (Wald $\chi^2 = 6.2$, $p = 0.013$, OR [95%CI] = 0.63 [0.44, 0.90]) and concomitant benzodiazepine medication (Wald $\chi^2 = 5.7$, $p = 0.017$, OR [95%CI] = 0.24 [0.07, 0.77]).

In the 90-day model, across the whole sample, the prevalence of drug use disorder was higher in Class 1 than in Class 2 ($p = 0.038$). Tendencies were observed for employment status ($p = 0.051$), number of depressive episodes ($p = 0.071$) and polarity ($p = 0.088$; Table 3).

The logistic regression showed significant effects of polarity, drug use disorder and employment status. Patients with bipolar TRD were more likely to be in Class 1 than patients with unipolar TRD (Wald $\chi^2 = 6.6$, p = 0.010, OR [95%CI] = 4.03 [1.39, 11.70]). Drug use disorder increased the odds of belonging to Class 1 (Wald $\chi^2 = 5.9$, $p = 0.015$, OR [95%CI] = 5.51 [1.40, 21.78]). Patients with a professional activity were more likely to be in Class 1 than unemployed patients (Wald $\chi^2 = 7.7$, $p = 0.005$, OR [95%CI] = 7.41 [1.81, 30.21]); the difference between patients with a professional activity and retired patients almost reached significance (Wald $\chi^2 = 3.0$, $p = 0.081$, OR [95%CI] = 4.07 [0.84, 19.69]) while the odds did not differ between unemployed and retired patients ($p = 0.308$).

3.4. ROC analysis

AUC were significantly higher than 0.5 from the MADRS assessment following the first administration (T1) for the prediction of classes from both the 30-day and 90-day models (Table 4).

Aiming to identify the best time-point compromise, we looked at the evolution of accuracy between each assessment. For classes identified in the 30-day model, we observed the highest increase (+9.8 %) between the T2 and T3 assessments: the MADRS score at T3 (after three administrations) predicted the class with an accuracy of 85.7 % (Table 4). More specifically, a MADRS score $\leq$ 18 at T3 was associated with a higher chance of belonging to Class 1 in the 30-day model (OR [95%CI] = 34.72 [11.57, 104.17]).

For classes identified in the 90-day model, it is between the T1 and T2 assessments that we observed the highest increase in accuracy (+7.7 %). The MADRS score at T2 (after only two administrations) predicted the class with an accuracy of 80.0 % (Table 4). More specifically, a MADRS score $\leq$ 22 at T2 was associated with a higher chance of belonging to Class 1 in the 90-day model (OR [95%CI] = 21.25 [7.11, 63.51]).

4. Discussion

In the present longitudinal study, we identified two classes of

Table 2
30-day model: demographics and disease characteristics for identified latent classes.

	All Patients (N = 105)			Original sample (N = 50)			Confirmatory sample (N = 55)		
	Class 1	Class 2	p	Class 1	Class 2	p	Class 1	Class 2	p
	(*N* = 43)	(*N* = 62)		(*N* = 15)	(*N* = 35)		(*N* = 28)	(*N* = 27)	
Demographic characteristics									
Age, mean (SD)	49.3 (15.5)	53.2 (17.9)	0.251	48.7 (16.4)	55.6 (16.2)	0.177	49.5 (15.3)	50 (19.8)	0.929
Gender, females	26 (60.5 %)	42 (67.7 %)	0.443	10 (66.7 %)	25 (71.4 %)	0.736	16 (57.1 %)	17 (63.0 %)	0.660
BMI, mean (SD)	24.9 (6.0)	24.9 (5.1)	0.971	25.1 (6.5)	24.3 (4.3)	0.637	24.7 (5.7)	26.1 (6.6)	0.568
Marital status			0.429			0.686			0.273
Single	12 (27.9 %)	16 (25.8 %)		2 (13.3 %)	8 (22.9 %)		10 (35.7 %)	8 (29.6 %)	
Widowed / Divorced	9 (20.9 %)	20 (32.3 %)		4 (26.7 %)	10 (28.6 %)		5 (17.9 %)	10 (37.0 %)	
Couple	22 (51.2 %)	26 (41.9 %)		9 (60.0 %)	17 (48.6 %)		13 (46.4 %)	9 (33.3 %)	
Employment status			0.112			0.207			0.205
Retired	5 (11.6 %)	15 (24.2 %)		1 (6.7 %)	10 (28.6 %)		4 (14.3 %)	5 (18.5 %)	
Off work or invalidity	26 (60.5 %)	38 (61.3 %)		12 (80.0 %)	20 (57.1 %)		14 (50.0 %)	18 (66.7 %)	
Regular	12 (27.9 %)	9 (14.5 %)		2 (13.3 %)	5 (14.3 %)		10 (35.7 %)	4 (14.8 %)	
Tobacco			0.488			0.240			0.194
Never	31 (72.1 %)	44 (71.0 %)		14 (93.3 %)	26 (74.3 %)		17 (60.7 %)	18 (66.7 %)	
Weaned	8 (18.6 %)	8 (12.9 %)		0 (0.0 %)	5 (14.3 %)		8 (28.6 %)	3 (11.1 %)	
Active	4 (9.3 %)	10 (16.1 %)		1 (6.7 %)	4 (11.4 %)		3 (10.7 %)	6 (22.2 %)	
Characteristics of the current depressive episode									
Current suicidal ideation	37 (86.0 %)	42 (67.7 %)	0.040	9 (60.0 %)	17 (48.6 %)	0.545	28 (100.0 %)	25 (92.6 %)	0.236
Maudsley			0.047			0.265			0.147
Acute (≤ 12 months)	29 (67.4 %)	27 (43.5 %)		10 (66.7 %)	15 (42.9 %)		19 (67.9 %)	12 (44.4 %)	
Sub-Acute (12–24 months)	4 (9.3 %)	13 (21.0 %)		3 (20.0 %)	9 (25.7 %)		1 (3.6 %)	4 (14.8 %)	
Chronic (≥ 24 months)	10 (23.3 %)	22 (35.5 %)		2 (13.3 %)	11 (31.4 %)		8 (28.6 %)	11 (40.7 %)	
Maudsley Total, mean (SD)	8.2 (2.2)	9.3 (2.2)	0.010	7.1 (2.2)	8.9 (2.0)	0.009	8.7 (2.0)	9.9 (2.2)	0.056
No. of current treatments, mean (SD)	5.0 (3.1)	6.1 (4.2)	0.302	4.0 (3.3)	4.9 (3.3)	0.377	5.6 (2.9)	7.7 (4.9)	0.065
Disease features									
No. of hospitalizations, mean (SD)	2.6 (1.9)	4.1 (3.6)	0.073	2.3 (2.8)	3.9 (3.8)	0.159	2.7 (1.4)	4.3 (3.4)	0.026
No. of episodes, mean (SD)	3.2 (1.7)	4.6 (2.9)	0.008	3.0 (1.8)	4.3 (2.5)	0.070	3.3 (1.7)	4.9 (3.3)	0.028
Lifetime duration of depression			0.082			0.415			0.151
< 2 years	8 (18.6 %)	3 (4.9 %)		2 (13.3 %)	2 (5.7 %)		6 (21.4 %)	1 (3.8 %)	
2–5 years	15 (34.9 %)	24 (39.3 %)		8 (53.3 %)	15 (42.9 %)		7 (25.0 %)	9 (34.6 %)	
>5 years	20 (46.5 %)	34 (55.7 %)		5 (33.3 %)	18 (51.4 %)		15 (53.6 %)	16 (61.5 %)	
Polarity			0.095			0.747			0.097
Unipolar	24 (55.8 %)	45 (72.6 %)		10 (66.7 %)	25 (71.4 %)		14 (50.0 %)	20 (74.1 %)	
Bipolar	19 (44.2 %)	17 (27.4 %)		5 (33.3 %)	10 (28.6 %)		14 (50.0 %)	7 (25.9 %)	
Comorbidity									
Personality disorder	6 (14.0 %)	13 (21.0 %)	0.444	3 (20.0 %)	11 (31.4 %)	0.507	3 (10.7 %)	2 (7.4 %)	1.000
Alcohol use disorder	6 (14.0 %)	8 (12.9 %)	1.000	3 (20.0 %)	6 (17.1 %)	1.000	3 (10.7 %)	2 (7.4 %)	1.000
Drug use disorder	10 (23.3 %)	9 (14.5 %)	0.306	4 (26.7 %)	7 (20.0 %)	0.713	6 (21.4 %)	2 (7.4 %)	0.252
Suicide attempt	21 (48.8 %)	28 (45.2 %)	0.843	6 (40.0 %)	14 (40.0 %)	1.000	15 (53.6 %)	14 (51.9 %)	1.000
Cardiovascular disorder	7 (16.3 %)	17 (27.4 %)	0.239	3 (20.0 %)	14 (40.0 %)	0.209	4 (14.3 %)	3 (11.1 %)	1.000
Neurological disorder	3 (7.0 %)	8 (12.9 %)	0.519	0 (0.0 %)	3 (8.6 %)	0.545	3 (10.7 %)	5 (18.5 %)	0.469
Obstructive sleep apnea	5 (11.6 %)	5 (8.1 %)	0.737	2 (13.3 %)	4 (11.4 %)	1.000	3 (10.7 %)	1 (3.7 %)	0.611
Endocrine disease	8 (18.6 %)	13 (21.0 %)	0.809	2 (13.3 %)	8 (22.9 %)	0.702	6 (21.4 %)	5 (18.5 %)	1.000
Dyslipidemia	4 (9.3 %)	6 (9.7 %)	1.000	1 (6.7 %)	4 (11.4 %)	1.000	3 (10.7 %)	2 (7.4 %)	1.000
Previous stroke	0 (0.0 %)	2 (3.2 %)	0.512	0 (0.0 %)	1 (2.9 %)	1.000	0 (0.0 %)	1 (3.7 %)	0.491
Family history									
Alcohol use disorder	4 (9.3 %)	6 (9.7 %)	1.000	3 (20.0 %)	4 (11.4 %)	0.415	1 (3.6 %)	2 (7.4 %)	0.611
Major depressive episodes	25 (58.1 %)	38 (61.3 %)	0.840	10 (66.7 %)	20 (57.1 %)	0.754	15 (53.6 %)	18 (66.7 %)	0.412
Treatment									
Antidepressants			0.832			0.414			0.952
Only one AD	24 (68.6 %)	37 (68.5 %)		12 (92.3 %)	24 (82.8 %)		12 (54.5 %)	13 (52.0 %)	
Two AD	8 (22.9 %)	14 (25.9 %)		1 (7.7 %)	5 (17.2 %)		7 (31.8 %)	9 (36.0 %)	
Three AD	3 (8.6 %)	3 (5.6 %)		0 (0.0 %)	0 (0.0 %)		3 (13.6 %)	3 (12.0 %)	
Lamotrigine	9 (20.9 %)	12 (19.4 %)	1.000	2 (13.3 %)	6 (17.1 %)	1.000	7 (25.0 %)	6 (22.2 %)	1.000
Lithium	15 (34.9 %)	9 (14.5 %)	0.019	2 (13.3 %)	2 (5.7 %)	0.574	13 (46.4 %)	7 (25.9 %)	0.162
Benzodiazepine	8 (18.6 %)	33 (53.2 %)	<0.001	4 (26.7 %)	21 (60.0 %)	0.062	4 (14.3 %)	12 (44.4 %)	0.019
Atypical antipsychotics	15 (34.9 %)	16 (25.8 %)	0.386	4 (26.7 %)	2 (5.7 %)	0.058	11 (39.3 %)	14 (51.9 %)	0.422
Electroconvulsive therapy									
Lifetime	6 (14.0 %)	23 (37.1 %)	0.014	1 (6.7 %)	12 (34.3 %)	0.076	5 (17.9 %)	11 (40.7 %)	0.080
Current episode	5 (11.6 %)	13 (21.0 %)	0.294	0 (0.0 %)	7 (20.0 %)	0.087	5 (17.9 %)	6 (22.2 %)	0.746
Response									
MADRS at baseline, mean (SD)	33.4 (5.6)	33.4 (6.2)	0.984	31.8 (5.1)	33.1 (6.5)	0.510	34.3 (5.8)	33.8 (5.9)	0.766
MADRS at T7, mean (SD)	9.7 (5.7)	22.8 (9.6)	<0.001	8.9 (5.7)	19.6 (9.2)	<0.001	10.1 (5.7)	26.8 (8.7)	<0.001
MADRS final, mean (SD)	11.5 (9.3)	22.3 (11.3)	<0.001	12.4 (12.7)	20.4 (11.6)	0.035	11.0 (7.0)	24.7 (10.6)	<0.001
Responders	38 (88.4 %)	17 (27.4 %)	<0.001	13 (86.7 %)	14 (40.0 %)	0.004	25 (89.3 %)	3 (11.1 %)	<0.001
Remitters	30 (69.8 %)	10 (16.1 %)	<0.001	11 (73.3 %)	9 (25.7 %)	0.004	19 (67.9 %)	1 (3.7 %)	<0.001

Unless "Mean (SD)" is stated, values correspond to No. (%).
AD: antidepressant; BMI: body mass index; df: degree of freedom; MADRS: Montgomery-Asberg depression rating scale; p: p-value; SD: standard deviation; T7: MADRS score at the eighth assessment (after seven administrations) used to define response and remission.

Table 3
90-day model: demographics and disease characteristics for identified latent classes.

	All Patients (N = 105)			Original sample (N = 50)			Confirmatory sample (N = 55)		
	Class 1	Class 2	p	Class 1	Class 2	p	Class 1	Class 2	p
	(*N* = 66)	(*N* = 39)		(N = 35)	(N = 15)		(*N* = 31)	(*N* = 24)	
Demographic characteristics									
Age, mean (SD)	50.9 (16.5)	52.6 (18.0)	0.624	52.9 (17.5)	55.1 (14.0)	0.671	48.7 (15.3)	51.1 (20.2)	0.622
Gender, females	41 (62.1 %)	27 (69.2 %)	0.461	24 (68.6 %)	11 (73.3 %)	0.736	17 (54.8 %)	16 (66.7 %)	0.375
BMI, mean (SD)	25.5 (5.5)	23.9 (5.2)	0.240	25.5 (5.3)	22.5 (3.9)	0.068	25.4 (6.2)	25.3 (6.1)	0.959
Marital status			0.137			0.428			0.321
Single	18 (27.3 %)	10 (25.6 %)		7 (20.0 %)	3 (20.0 %)		11 (35.5 %)	7 (29.2 %)	
Widowed / Divorced	14 (21.2 %)	15 (38.5 %)		8 (22.9 %)	6 (40.0 %)		6 (19.4 %)	9 (37.5 %)	
Couple	34 (51.5 %)	14 (35.9 %)		20 (57.1 %)	6 (40.0 %)		14 (45.2 %)	8 (33.3 %)	
Employment status			0.051			0.143			0.146
Retired	12 (18.2 %)	8 (20.5 %)		8 (22.9 %)	3 (20.0 %)		4 (12.9 %)	5 (20.8 %)	
Off work or invalidity	36 (54.5 %)	28 (71.8 %)		20 (57.1 %)	12 (80.0 %)		16 (51.6 %)	16 (66.7 %)	
Regular	18 (27.3 %)	3 (7.7 %)		7 (20.0 %)	0 (0.0 %)		11 (35.5 %)	3 (12.5 %)	
Tobacco			0.805			0.788			0.861
Never	47 (71.2 %)	28 (71.8 %)		28 (80.0 %)	12 (80.0 %)		19 (61.3 %)	16 (66.7 %)	
Weaned	11 (16.7 %)	5 (12.8 %)		4 (11.4 %)	1 (6.7 %)		7 (22.6 %)	4 (16.7 %)	
Active	8 (12.1 %)	6 (15.4 %)		3 (8.6 %)	2 (13.3 %)		5 (16.1 %)	4 (16.7 %)	
Characteristics of the current depressive episode									
Current suicidal ideation	50 (75.8 %)	29 (74.4 %)	1.000	19 (54.3 %)	7 (46.7 %)	0.760	31 (100.0 %)	22 (91.7 %)	0.186
Maudsley			0.477			0.571			0.367
Acute (≤ 12 months)	38 (57.6 %)	18 (46.2 %)		18 (51.4 %)	7 (46.7 %)		20 (64.5 %)	11 (45.8 %)	
Sub-Acute (12–24 months)	9 (13.6 %)	8 (20.5 %)		7 (20.0 %)	5 (33.3 %)		2 (6.5 %)	3 (12.5 %)	
Chronic (≥ 24 months)	19 (28.8 %)	13 (33.3 %)		10 (28.6 %)	3 (20.0 %)		9 (29.0 %)	10 (41.7 %)	
Maudsley Total, mean (SD)	8.6 (2.2)	9.2 (2.3)	0.177	8.3 (2.3)	8.6 (2.2)	0.623	9 (2.1)	9.7 (2.3)	0.312
No. of current treatments, mean (SD)	5.4 (3.8)	6.1 (3.9)	0.350	4.6 (3.5)	4.7 (3.0)	0.971	6.3 (4.0)	7.0 (4.2)	0.540
Disease features									
No. of hospitalizations, mean (SD)	3.1 (3.1)	4.1 (3.0)	0.114	2.9 (3.5)	4.5 (3.6)	0.165	3.2 (2.7)	3.8 (2.6)	0.414
No. of episodes, mean (SD)	3.8 (2.8)	4.3 (2.1)	0.071	3.7 (2.3)	4.5 (2.6)	0.232	4.0 (3.3)	4.2 (1.8)	0.172
Lifetime duration of depression			0.379			0.792			0.079
< 2 years	9 (13.6 %)	2 (5.3 %)		3 (8.6 %)	1 (6.7 %)		6 (19.4 %)	1 (4.3 %)	
2–5 years	23 (34.8 %)	16 (42.1 %)		17 (48.6 %)	6 (40.0 %)		6 (19.4 %)	10 (43.5 %)	
> 5 years	34 (51.5 %)	20 (52.6 %)		15 (42.9 %)	8 (53.3 %)		19 (61.3 %)	12 (52.2 %)	
Polarity			0.088			0.502			0.098
Unipolar	39 (59.1 %)	30 (76.9 %)		23 (65.7 %)	12 (80.0 %)		16 (51.6 %)	18 (75.0 %)	
Bipolar	27 (40.9 %)	9 (23.1 %)		12 (34.3 %)	3 (20.0 %)		15 (48.4 %)	6 (25.0 %)	
Comorbidity									
Personality disorder	12 (18.2 %)	7 (17.9 %)	1.000	8 (22.9 %)	6 (40.0 %)	0.304	4 (12.9 %)	1 (4.2 %)	0.373
Alcohol use disorder	9 (13.6 %)	5 (12.8 %)	1.000	6 (17.1 %)	3 (20.0 %)	1.000	3 (9.7 %)	2 (8.3 %)	1.000
Drug use disorder	16 (24.2 %)	3 (7.7 %)	0.038	9 (25.7 %)	2 (13.3 %)	0.468	7 (22.6 %)	1 (4.2 %)	0.119
Suicide attempt	31 (47.0 %)	18 (46.2 %)	1.000	12 (34.3 %)	8 (53.3 %)	0.228	19 (61.3 %)	10 (41.7 %)	0.180
Cardiovascular disorder	17 (25.8 %)	7 (17.9 %)	0.472	13 (37.1 %)	4 (26.7 %)	0.533	4 (12.9 %)	3 (12.5 %)	1.000
Neurological disorder	6 (9.1 %)	5 (12.8 %)	0.532	1 (2.9 %)	2 (13.3 %)	0.211	5 (16.1 %)	3 (12.5 %)	1.000
Obstructive sleep apnea	8 (12.1 %)	2 (5.1 %)	0.316	5 (14.3 %)	1 (6.7 %)	0.654	3 (9.7 %)	1 (4.2 %)	0.624
Endocrine disease	12 (18.2 %)	9 (23.1 %)	0.617	6 (17.1 %)	4 (26.7 %)	0.462	6 (19.4 %)	5 (20.8 %)	1.000
Dyslipidemia	6 (9.1 %)	4 (10.3 %)	1.000	4 (11.4 %)	1 (6.7 %)	1.000	2 (6.5 %)	3 (12.5 %)	0.643
Previous stroke	0 (0.0 %)	2 (5.1 %)	0.136	0 (0.0 %)	1 (6.7 %)	0.300	0 (0.0 %)	1 (4.2 %)	0.436
Family history									
Alcohol use disorder	6 (9.1 %)	4 (10.3 %)	1.000	4 (11.4 %)	3 (20.0 %)	0.415	2 (6.5 %)	1 (4.2 %)	1.000
Major depressive episodes	41 (62.1 %)	22 (56.4 %)	0.681	23 (65.7 %)	7 (46.7 %)	0.228	18 (58.1 %)	15 (62.5 %)	0.787
Treatment									
Antidepressants			0.439			0.350			0.250
Only one AD	36 (67.9 %)	25 (69.4 %)		23 (82.1 %)	13 (92.9 %)		13 (52.0 %)	12 (54.5 %)	
Two AD	12 (22.6 %)	10 (27.8 %)		5 (17.9 %)	1 (7.1 %)		7 (28.0 %)	9 (40.9 %)	
Three AD	5 (9.4 %)	1 (2.8 %)		0 (0.0 %)	0 (0.0 %)		5 (20.0 %)	1 (4.5 %)	
Lamotrigine	11 (16.7 %)	10 (25.6 %)	0.316	3 (8.6 %)	5 (33.3 %)	0.043	8 (25.8 %)	5 (20.8 %)	0.756
Lithium	17 (25.8 %)	7 (17.9 %)	0.472	3 (8.6 %)	1 (6.7 %)	1.000	14 (45.2 %)	6 (25.0 %)	0.162
Benzodiazepine	22 (33.3 %)	19 (48.7 %)	0.148	17 (48.6 %)	8 (53.3 %)	1.000	5 (16.1 %)	11 (45.8 %)	0.034
Atypical antipsychotics	19 (28.8 %)	12 (30.8 %)	0.829	6 (17.1 %)	0 (0.0 %)	0.160	13 (41.9 %)	12 (50.0 %)	0.594
Electroconvulsive therapy									
Lifetime	15 (22.7 %)	14 (35.9 %)	0.177	8 (22.9 %)	5 (33.3 %)	0.493	7 (22.6 %)	9 (37.5 %)	0.249
Current episode	10 (15.2 %)	8 (20.5 %)	0.593	4 (11.4 %)	3 (20.0 %)	0.415	6 (19.4 %)	5 (20.8 %)	1.000
Response									
MADRS at baseline, mean (SD)	32.9 (5.5)	34.1 (6.6)	0.325	32.0 (5.1)	34.2 (7.9)	0.253	34.0 (5.9)	34.1 (5.8)	0.942
MADRS at T7, mean (SD)	11.8 (6.5)	27.0 (8.7)	<0.001	12.0 (6.4)	26.8 (7.6)	<0.001	11.6 (6.7)	27.1 (9.5)	<0.001
MADRS final, mean (SD)	12.5 (9.2)	27.0 (9.7)	<0.001	13.3 (10.8)	28.9 (8.7)	<0.001	11.5 (7.1)	25.8 (10.4)	<0.001
Responders	50 (75.8 %)	5 (12.8 %)	<0.001	25 (71.4 %)	2 (13.3 %)	<0.001	25 (80.6 %)	3 (12.5 %)	<0.001
Remitters	38 (57.6 %)	2 (5.1 %)	<0.001	20 (57.1 %)	0 (0.0 %)	<0.001	18 (58.1 %)	2 (8.3 %)	<0.001

Unless "Mean (SD)" is stated, values correspond to No. (%).
AD: antidepressant; BMI: body mass index; MADRS: Montgomery-Asberg depression rating scale; p: p-value; SD: standard deviation; T7: MADRS score at the eighth assessment (after seven administrations) used to define response and remission.

Table 4
Predictability of outcome by MADRS scores at each administration time.

MADRS	Time (days)	AUC			Cut-off	Youden's	Sensitivity	Specificity	PPV	NPV	Accuracy	OR	
assessment	Median [IQR]	Value	[95 % CI]	p								Value	[95 % CI]
Class in the 30-day model													
Baseline	0 [0, 0]	0.507	[0.395, 0.619]	0.450									
T1	3 [3, 4]	0.744	[0.644, 0.844]	<0.001	25	0.45	76.7 %	67.7 %	62.3 %	80.8 %	71.4 %	6.93	[2.86, 16.79]
T2	7 [7, 7]	0.854	[0.780, 0.928]	<0.001	21	0.57	81.4 %	75.8 %	70.0 %	85.5 %	78.1 %	13.72	[5.23, 35.94]
T3	10 [10, 11]	0.910	[0.853, 0.967]	<0.001	18	0.71	83.7 %	87.1 %	81.8 %	88.5 %	85.7 %	34.72	[11.57, 104.17]
T4	14 [14, 14]	0.950	[0.907, 0.993]	<0.001	17	0.81	90.7 %	90.3 %	86.7 %	93.3 %	90.5 %	91.00	[24.08, 343.93]
T5	17 [17, 19]	0.896	[0.839, 0.953]	<0.001	13	0.62	69.8 %	91.9 %	85.7 %	81.4 %	82.9 %	26.33	[8.57, 80.88]
T6	21 [21,21]	0.869	[0.802, 0.936]	<0.001	19	0.58	90.7 %	67.7 %	66.1 %	91.3 %	77.1 %	20.48	[6.43, 65.24]
Class in the 90-day model													
Baseline	0 [0, 0]	0.549	[0.431, 0.667]	0.211									
T1	3 [3, 4]	0.768	[0.678, 0.858]	<0.001	25	0.52	69.7 %	82.1 %	86.8 %	61.5 %	74.3 %	10.51	[3.98, 27.79]
T2	7 [7, 7]	0.845	[0.769, 0.921]	<0.001	22	0.63	75.8 %	87.2 %	90.9 %	68.0 %	80.0 %	21.25	[7.11, 63.51]
T3	10 [10, 11]	0.829	[0.747, 0.911]	<0.001	22	0.67	77.3 %	89.7 %	92.7 %	70.0 %	81.9 %	29.73	[9.10, 97.13]
T4	14 [14, 14]	0.886	[0.819, 0.953]	<0.001	22	0.66	81.8 %	84.6 %	90.0 %	73.3 %	82.9 %	24.76	[8.48, 72.30]
T5	17 [17, 19]	0.908	[0.845, 0.971]	<0.001	22	0.72	92.4 %	79.5 %	88.4 %	86.1 %	87.6 %	47.25	[14.26, 156.57]
T6	21 [21, 21]	0.916	[0.863, 0.969]	<0.001	18	0.68	80.3 %	87.2 %	91.4 %	72.3 %	82.9 %	27.72	[9.06, 84.76]

A p-value lower than 0.05 indicates that the AUC significantly differs from 0.5. A positive test is defined as a MADRS score equal to or lower than the cut-off.
AUC: area under the curve; CI: confidence interval; IQR: interquartile range; MADRS: Montgomery-Asberg depression rating scale; NPV: negative predictive value; OR: odds ratio; p: *p*-value; PPV: positive predictive value.

patients with TRD characterized by distinct trajectories of response to esketamine. The first class mostly gathered responders while non-responders were mostly in the second class. We were able to replicate these findings by applying the latent class mixed model on an independent cohort. A few baseline factors differed between patients from the two classes. When considering the evolution of MADRS scores over 30 days, concomitant benzodiazepine medication and a higher number of depressive episodes decreased the odds of belonging to Class 1, i.e. the class characterized by a faster and greater response. In the longer term, over 90 days, the odds of belonging to the first class were increased by bipolarity, drug use disorder and professional activity. Besides baseline characteristics, the early response to esketamine was highly predictive of the trajectory: after only two administrations, the MADRS score predicted the 90-day trajectory with an accuracy of 80.0 %.

The best-fitting latent class model defined two distinct classes of patients. The trajectory characterizing the first class depicted a fast and complete treatment response, while the decrease in MADRS scores in the second class was slower and unstable. From two to nine classes have been identified in other studies on treatment response in depression (Goerigk et al., 2021; Gueorguieva et al., 2011; Kelley et al., 2018; Larsen et al., 2020; Maalouf et al., 2012; Rhebergen et al., 2015; Uher et al., 2011). Most commonly, three classes, corresponding to fast, slow and no response respectively, were identified (Goerigk et al., 2021; Larsen et al., 2020; Maalouf et al., 2012; Rhebergen et al., 2015). Our study is, as far as we know, the first one to use latent class analyses to evaluate esketamine treatment. Our model was consistent and reproducible across our two samples, but whether the existence of two response trajectories is characteristic of esketamine and can be generalized needs to be confirmed.

In clinical trials, between 53.1 % and 78.4 % of patients responded to esketamine while remission rates ranged from 36.0 % to 52.5 % (Fedgchin et al., 2019; Popova et al., 2019; Wajs et al., 2020). Our observed response and remission rates (52.4 % and 38.1 %, respectively) come close to these ranges. A difference between our study and clinical trials is that only patients with unipolar TRD were included in clinical trials, while 36 (34.3 %) patients in our study suffered from bipolar TRD. We found that esketamine was effective in bipolar TRD and did not notice any new manic episodes during the period of the study. This is in line with recent reports on efficacy and safety of esketamine in bipolar TRD (Delfino et al., 2021; Martinotti et al., 2023; Surjan et al., 2022).

Some of the predictive factors we observed were expected or previously raised (number of depressive episodes, professional activity and concomitant benzodiazepine medication), while other ones (drug use disorder and polarity) might be new and challenge what is currently known. In a recent post-hoc pooled analysis of two trials of intranasal esketamine, professional activity was, along with a younger age and fewer failed ADs, a significant positive predictor of response and remission (Turkoz et al., 2023). The use of benzodiazepine influenced the trajectory of response, decreasing by 76 % the odds of belonging to the first class over the first 30 days. This result concurs with a previous report that concomitant benzodiazepine medication dampens the antidepressant effect of ketamine (Andrashko et al., 2020). However, in a randomized controlled trial conducted in patients with major depressive disorder and acute suicidal ideation or behavior, benzodiazepines did not significantly affect the rapid antidepressant effect of esketamine (Diekamp et al., 2021). The discordance between our results may ensue from the differences between our samples, i.e. patients with major depressive disorder and acute suicidal ideation or behavior in

experimental settings versus patients with TRD in real-world settings, or from differences between the study designs since we observed an effect of benzodiazepine on the 30-day trajectory of response while they studied the effects of esketamine in the 24 h following the first administration. Nevertheless, this observation calls for further investigations because confirming a negative effect of benzodiazepines on esketamine efficacy could lead to recommendations to avoid concomitant benzodiazepine medication. Before that, a controlled study is needed as chance-finding is always possible, especially as the initial negative effect of benzodiazepine did not hold in the 90-day model. Bipolar disorder and drug use disorder were surprisingly associated with a better outcome, suggesting that these disorders may not be contraindications to esketamine treatment. However, further investigations are required to assess in experimental conditions the effect of polarity and drug use disorder on esketamine efficacy. Testing our observations in controlled studies is all the more important because of the absence of replication between the 30-day and 90-day models, which implies a high risk of spurious finding.

In addition to baseline characteristics, the trajectory of response can be predicted from the MADRS score after the first esketamine administrations. Early symptomatic improvements have previously been reported as a predictor of response in a study on intravenous ketamine: improvement after one or two ketamine infusions was associated with greater antidepressant effects following four ketamine infusions received over one to two weeks (Lipsitz et al., 2021). This finding echoes ours, although the time frame in our study was longer. Indeed, our results indicate for example that, after two esketamine administrations, the MADRS score predicts the 90-day trajectory with an accuracy of 80.0 %. More specifically, a MADRS score equal to or lower than 22 is associated with a 90.9 % chance to belong to Class 1, while a MADRS score higher than 22 is associated with a 68.0 % probability to belong to Class 2. Although further research in experimental settings is required to confirm the cutoffs, this finding suggests that, if the score is higher than the cutoff, it may be better to discontinue the treatment to limit unnecessary costs and, without further delay, guide the patient towards other therapeutic options with higher chances of success. It is also interesting to note that the cutoffs presented here are selected based on the Youden's index which maximizes the combination of sensitivity and specificity, but other criteria may be used to favor either sensitivity or specificity (Zou et al., 2013). For instance, favoring sensitivity would reduce the false negative rate, i.e. the risk to discontinue the treatment in patients who could have responded. Rather than a unique cutoff, defining different thresholds and their associated false negative risks is another possibility.

Strengths of this study include being based on real-world data, which limits selection bias: the samples are representative of patients treated at both centers for TRD, in contrast to clinical trials where inclusion and exclusion criteria are stricter. Patients consulting for TRD are in average older and in poorer health than patients included in clinical trials (Cepeda et al., 2021). Another strength is that latent class analyses are highly relevant in clinical studies due to their ability to identify different trajectories of response based on the evolution of symptoms (Nagin and Odgers, 2010). These analyses are more and more common in studies assessing interindividual differences in treatment response (Nagin and Odgers, 2010; van de Schoot et al., 2017). Our study is also strengthened by the nested confirmatory study conducted in an independent cohort which replicates and confirms our findings.

Limitations include that our study was not placebo-controlled, we therefore cannot specifically attribute observed effects to esketamine. Indeed, it is estimated that approximately 30 % of patients in antidepressant and antipsychotic trials respond to placebo treatment (Huneke et al., 2020), which suggests that our results would benefit from a confirmation in future placebo-controlled studies. Nevertheless, our study was conducted in two different services with different patients and care strategies, and results were replicated. The second limitation concerns the generalizability of our findings since both samples were recruited in the same university hospital in Paris: patients come from the same geographical area and can therefore be expected to share similarities when it comes to sociodemographic factors or culture. However, the two samples were independent and significantly differed. Third, considering the large heterogeneity of the sample, the sample size may have been insufficient to detect other less frequent trajectories and more predictive factors, explaining why we merged samples in order to increase the chances to detect any predictive factor. More trajectories and predictive factors may have been found in a larger sample. Yet, we have here one of the largest samples in an open trial regarding esketamine. Finally, this is an observational study. Our findings therefore need to be confirmed in experimental, more controlled, settings.

In conclusion, in addition to considering some baseline factors such as concomitant benzodiazepine use which may influence response to esketamine, we propose to base the clinical decision to continue the treatment on early effects, since the MADRS score after the first administrations can predict the most plausible trajectory of response. Optimal threshold scores need to be determined and confirmed in further studies.

CRediT authorship contribution statement

Philip Gorwood designed the study, participated in the interpretation of data and in the writing of the manuscript. Isaure Estrade collected data from the CMME department, reviewed the literature, and participated in the interpretation of data. Michel Danon participated in the interpretation of data and in the drafting of the manuscript. Rebecca Perrain collected data from the CMME department, participated in the interpretation of data and in the drafting of the manuscript. Lila Mekaoui collected data from the CMME department, supervised the collection of data in the same department, participated in the interpretation of data and in critical revision of the manuscript. Daphnée Poupon created the first draft of the manuscript. Emmanuelle Advenier-Iakovlev and Sylvain Leroy participated in the export of data and provided the esketamine by ensuring the medication process in accordance with the summary of product characteristics. Rossella Letizia Mancusi analyzed the data. Anne-Cécile Petit collected data from the SHU department, participated in the interpretation of data and the writing of the manuscript. Vincent Sylvestre collected data from the SHU department. Fabien Vinckier participated in the interpretation of data and in critical revision of the manuscript. Raphaël Gaillard participated in critical revision of the manuscript. Pierre de Maricourt collected data from the Pôle Hospitalo-Universitaire department and participated in the interpretation of data and in critical revision of the manuscript.

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Declaration of competing interest

PG received during the last 5 years fees for presentations at congresses or participation in scientific boards from Angelini, Janssen, Lundbeck, Otsuka and Viatris. ACP and PM received fees for presentations and congress participation from Janssen. RP has been invited by Janssen to a congress. LM has received honoraria or consulting fees from Bristol-Meyers-Squibb, Janssen, Servier, Lilly and Otsuka. RG has received compensation as a member of the scientific advisory board of Janssen, Lundbeck, Roche, SOBI, and Takeda, has served as a consultant and/or speaker for AstraZeneca, Boehringer Ingelheim, Pierre Fabre, Lilly, Lundbeck, LVMH, MAPREG, Novartis, Otsuka, Pileje, SANOFI, and Servier and received compensation. He has also received research support from Servier. FV has been invited to scientific meetings, consulted and/or served as a speaker, and received compensation from Lundbeck, Servier, Recordati, Janssen, Otsuka, LivaNova, Chiesi, and Rovi. He has received research support from LivaNova and Lundbeck. Other authors

declare no conflict of interest.

Data availability

Data are available from the corresponding author on reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.09.030.

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