PM. Llorca [1], **A. Sauvaget** [2], **E. Olié** [3], **L. Samalin** [4], **P. de Maricourt** [5], **E. Gaudre Wattinne** [6], **H. Lacour** [7], **J. Dupin** [6], **C. Wicart** [6]

1. Service de Psychiatrie, CHU Clermont-Ferrand, Université Clermont Auvergne, CNRS, INP Clermont Auvergne, Institut Pascal (UMR 6602), Clermont-Ferrand, France ; 2. Nantes Université, CHU de Nantes - Laboratory "Movement, Interactions, Performance" (E.A. 4334), Faculty of Sport Sciences, University of Nantes ; 3. Centre Hospitalier Universitaire de Montpellier, Hôpital Lapeyronie, Psychiatric Emergency and Post Emergency Department, Pole Urgence, Montpellier, France ; 4. Service de psychiatrie, CHU de Clermont-Ferrand, Université de Clermont Auvergne, CNRS, IP, UMR 6602, Clermont-Ferrand, France ; 5. Hôpital Sainte Anne GHU Paris – Psychiatrie et neurosciences, Paris, France ; 6. Affaires médicales, Janssen Cilag, France ; 7. Heva, Vendargues, France

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Evolution of clinical dimensions and safety in patients with major depressive disorder treated by esketamine: the French real-world ELLIPSE study

INTRODUCTION

One-third of patients with major depressive disorder (MDD) do not respond to initial treatment (treatment-resistant depression [TRD]) [1-3]. Since 2019, esketamine nasal spray (ESK) was approved in adult TRD patients without response to a minimum of two antidepressant medications administered during an episode of moderate-to-severe depression [4, 5].

OBJECTIVES

The objectives of this work were:

- To describe treatments administered prior to and alongside ESK initiation.
- To provide a detailed analysis of the evolution of depressive symptoms using MADRS sub-items.
- To further assess the safety profile of ESK, with a particular focus on dissociative states and potential dependence.

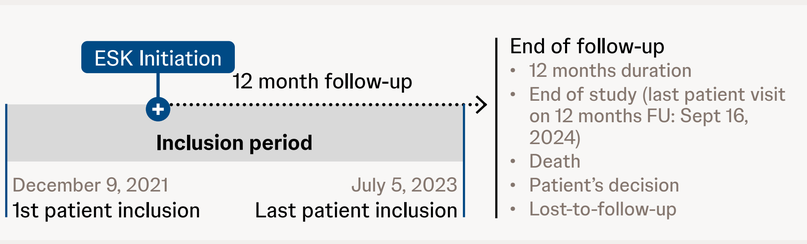
METHODS

ELLIPSE is a French prospective, multicenter, non-interventional study designed to describe patients presenting MDD treated with ESK, and for whom the decision to prescribe ESK was prior to the inclusion in the study. It was approved by the Sud-Méditerranée I ethics committee on September 27, 2021.

Study population

All patients who received at least one dose of ESK, who meet study inclusion/exclusion criteria:

- **Inclusion criteria:** adult (≥18 years) patients diagnosed with unipolar depression who not objected the collection of their data.
- **Exclusion criteria:** patients who have participated, or planned to participate, in a clinical trial at the time of enrollment or within the 30 days prior to enrollment.



Variables

Data were collected from physicians as part of routine clinical practice and from patients via self-questionnaires over the follow-up.

Well-conducted lines prior to ESK initiation were defined as at least one of the following: an antidepressant taken as monotherapy during at least 28 days (with or without augmentation), a combination of antidepressants (2 or more) taken during at least 28 days (with or without augmentation), at least 6 consecutive sessions of neurostimulation).

Response was defined as ≥50% decrease in MADRS score or MADRS score ≤10 over the follow-up. Remission was defined as MADRS score ≤10 over the follow-up.

CONCLUSION

ELLIPSE is the first prospective cohort of this scale to describe real-world treatment-resistant depression in France. All clinical dimensions assessed by the MADRS showed improvement over the follow-up period, offering valuable insights for clinical practice. No new safety signals were identified.

LIMITATIONS

While key limitations inherent to observational studies (such as selection, information bias, and a decrease of the number of patients treated by M6) were carefully mitigated, the evaluation of esketamine dependence relied on two non-specialized methods (a question in the CRF and AE report forms). Therefore, findings related to dependence should be interpreted with caution.

References

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Acknowledgement

Janssen would like to thank all the patients, psychiatrists and staff of the psychiatric units who took part in this study

RESULTS

Patients characteristics

- 200 patients were enrolled from 31 active centers (among 134 centers that ordered ESK) and followed for the treatment patterns and effectiveness analyses. 7 patients did not meet the inclusion/exclusion criteria and have only been conisdered in the safety analysis (n=207).
- Follow-up: median duration of 11.8 months (interquartile range: 6.0-12.2 months).

Table 1. Patients characteristics

	Total (N=200)
Demographics and physical examination	
Mean (SD) age, years	**46.6 (15.5)**
Female, n (%)	**113 (56.5)**
Lifetime history of depression	
Duration of depression, years, median (IQR)	**10.0 (3.2-22.9)**
Number of lifetime MDE (excluding the current MDE), mean (SD)	**3.0 (2.9)**
At least one suicide attempt in patients with at least one MDE (n=160), n (% of 200 patients)	**78 (39.0)**
Current MDE	
Current MDE duration, years, median (IQR)	**1.8 (0.9-3.2)**
Treatment-resistant (clinician's judgement), n (%)	**195 (97.5)**
At least one inpatient hospitalisation since start of MDE, n (%)	**115 (57.5)**
Total MADRS score	**N=198**
• Mean (SD)	31.9 (7.0)
• Mild depression, n (%)	8 (4.0)
• Moderate depression, n (%)	118 (59.6)
• Severe depression, n (%)	72 (36.4)
Comorbidities, at least one, n (%)	**144 (72.0)**
• Anxiety disorders	79 (54.9)
• Posttraumatic stress disorder	48 (33.3)
• Substance use-related disorders and addictive disorders	40 (27.8)

Treatment patterns

In the total population a median number of 3 (IQR: 2–5) well-conducted lines prior to ESK initiation was reported (18 missing). It included antidepressant (AD): monotherapy (64.5%), combined with augmentation (30.5%), combined with another antidepressant (29.5%), or both (37.0%); augmentation alone (31.5%); neurostimulation (22.5%) (Table 2).

Table 2. Well-conducted lines prior to ESK initiation during the current MDE

Details of well-conducted lines of AD	
Monotherapy AD	**129 (64.5)**
Monotherapy AD + augmentation	**61 (30.5)**
Combination AD	**59 (29.5)**
Combination AD + augmentation	**74 (37.0)**
Monotherapy augmentation	**63 (31.5)**
Combination augmentation	**18 (9.0)**
Neurostimulation	**45 (22.5)**

Almost all patients (95.5%) were receiving antidepressant treatment at the time of esketamine initiation (Table 3). SSRI (Selective Serotonin Reuptake Inhibitor) were reported in 50.0% (100/200) of the patients, while SNRI (Serotonin and Noradrenaline Reuptake Inhibitors) were reported in 47.0% (94/200), and 26.0% (52/200) received neither SSRI nor SNRI. An augmentation strategy was employed in 57.0% of patients).

Table 3. Concomitant pharmacologic treatments at esketamine initiation

	Prospective N=200
Antidepressants	**191 (95.5)**
SSRI	**100 (50.0)**
• Fluoxetine	47 (23.5)
• Sertraline	34 (17.0)
• Paroxetine	26 (13.0)
• Escitalopram	23 (11.5)
• Citalopram	2 (1.0)
• Fluvoxamine	2 (1.0)
SNRI	**94 (47.0)**
• Venlafaxine	74 (37.0)
• Duloxetine	24 (12.0)
• Milnacipran	9 (4.5)
Others	**135 (67.5)**
• Mirtazapine	54 (27.0)
• Vortioxetine	48 (24.0)
• Clomipramine	38 (19.0)
• Mianserin	29 (14.5)
• Amitriptyline	11 (5.5)
• Other	24 (12.0)
Augmentation strategy	**114 (57.0)**
Second generation antipsychotic	**69 (34.5)**
• Quetiapine	36 (18.0)
• Aripiprazole	22 (11.0)
• Olanzapine	17 (8.5)
• Risperidone	10 (5.0)
• Clozapine	3 (1.5)
Antiepileptic	**46 (23.0)**
Lithium	**40 (20.0)**
Other	**28 (14.0)**
Thyroid hormone	**3 (1.5)**

Evolution of MADRS

Mean baseline total MADRS score declined until reaching a plateau at M2 that persisted during the follow-up (Figure 1). Response and remission rates increased progressively until reaching a plateau at M2 (response: 55.2% / remission: 33.6%).

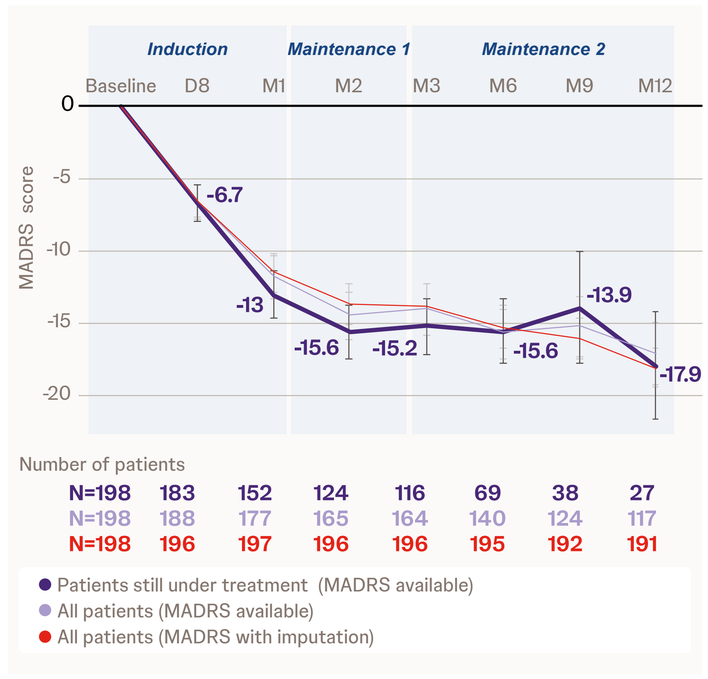

Figure 1. Mean absolute change in MADRS score

The tendency was consistent among all MADRS sub-items in patients still under treatment (Figure 2).

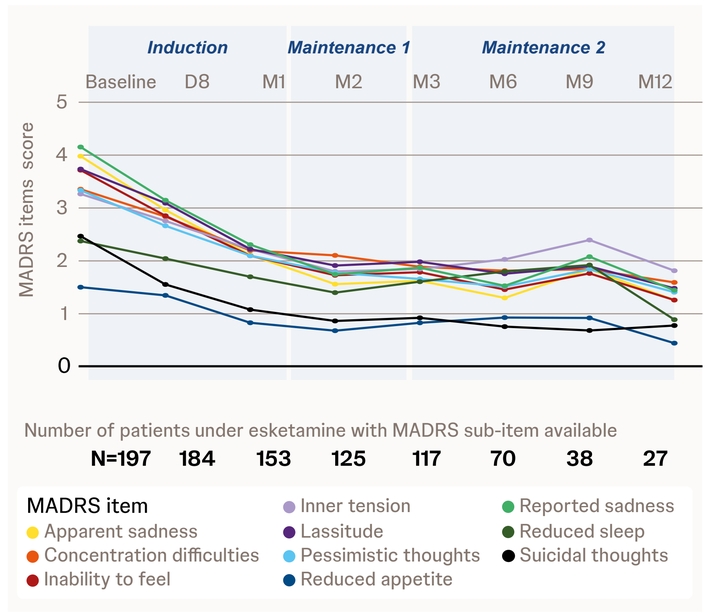

Figure 2. Mean MADRS sub-items in patients still under esketamine with MADRS available

Safety

1,263 AEs (adverse events) were identified in 136/207 (65.7%) patients. 1,071 AEs linked to the treatment in 99 (47.8%) patients. Dissociative states were reported in 29.5% of the cohort (61/207) (Table 4).

Table 4. Dissociatives states summary and outcomes

	Events (N)	Patients (N, %)
Dissociative states	**470**	**61**
Summary		
• Non serious	**470**	**61 (100.0)**
• Related to treatment	465	58 (95.1)
Ouctome		
• Recovered	**470**	**61 (100.0)**
• No change in treatment posology	466	60 (98.4)
• Dose decreased	3	3 (4.9)
• Treatment discontinuation	1	1 (1.6)

Then, to the question "What is your assessment of the presence of clinical signs of dependence in your patient regarding ESKETAMINE treatment?", twelve patients were reported as showing clinical signs of dependence on esketamine (11 mild [5.4%] - 1 moderate [0.5%] by the physician). Of these 12 patients, 9 showed transient signs while still being under treatment. 2 out of 12 showed signs of dependence only when treatment was discontinued. A single patient presented dependence signs from initiation to discontinuation. A single event was declared as an AE.

To the question, "Did the patient show clinical signs suggestive of withdrawal syndrome following discontinuation of treatment with ESKETAMINE or a reduction in dosage?", one patient (1/207, 0.5%) was reported with withdrawal symptoms at the M2 visit after discontinuing treatment after 28 days.