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Real world clinical practice, effectiveness and safety of esketamine nasal spray in MDD patients: the French ELLIPSE study

INTRODUCTION

Major depressive disorder (MDD) is the leading cause of disability worldwide [1]. About one third of patients with MDD fails to achieve remission despite treatment and can be considered as Treatment-Resistant patients (TRD) [2,3].

Since 2019, the nasal spray formulation of esketamine (ESK) has been approved for use in both the United States and Europe for adult patients diagnosed with TRD who have not shown adequate response to a minimum of two antidepressant medications, administered during an episode of moderate to severe depression [4,5]. ELLIPSE is the inaugural observational prospective study on ESK conducted in real-world settings in France.

The objective was to describe the profile of ESK patients, ESK modalities of use, patient management and outcomes in terms of efficacy and safety during the 12-month period following treatment initiation.

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.

- **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.

Patients were followed from ESK initiation for 12 months (last patient visit on 12 months FU: 16 Sept 2024), or patient's decision, lost to follow-up, or death, if it occurred earlier.

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

CONCLUSION

ELLIPSE is the first prospective cohort of this size to describe ESK in real-life conditions in TRD patients in France.

The results of the study are consistent with data from clinical trials [6] and real-world studies [7,8].

The characteristics of the patients treated, as well as the utilization practices, clinical effectiveness and safety profile of ESK confirm its place as a therapeutic strategy for resistant depression in France.

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RESULTS

Patients' characteristics

- 200 patients were enrolled from 31 active centers.
- Follow-up: median duration of 11.8 months (interquartile range: 6.0-12.2 months).

Table 1. Baseline characteristics at ESK initiation

Characteristics	Total (N=200)
Demographics and physical examination	
Age (years)	**46.6 (15.5)**
Mean (SD)	46.6 (15.5)
<65 years, n (%)	177 (88.5)
Women	**113 (56.5)**
Normal blood pressure, n (%)	**178/195 (91.3)**
Lifetime history of depression	
Duration of depression (years) (N=142) Mean (SD)	10 (3.2-22.8)
Number of lifetime MDE (excluding the current MDE)(N=198), Mean (SD)	3.0 (2.9)
Lifetime number of treatment-resistant episodes (failure of at least two treatment lines, excluding the current MDE) (N=158), Mean (SD)	1.8 (2.1)
At least one suicide attempt in patients with at least one MDE, n (%)	**78 (39.0)**
Current MDE	**200 (100.0)**
Current MDE duration (years) (N=184), median (IQR)	**3.0 (2.9)**
Major sub-type of MDE, n (%)	
Anxious	116 (58.0)
Melancholy	42 (21.0)
Atypical	12 (6.0)
At least one inpatient hospitalization since start of MDE, n (%)	**115 (57.5)**
Treatment-resistant (clinician's judgement), n (%)	**195 (97.5)**
Total MADRS at inclusion	**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)
EDC Severity (clinician's judgement), n (%)	
Mild	1 (0.5)
Moderate	63 (31.5)
Severe	136 (68.0)
Psychiatric comorbidities, n (%)	**144 (72.0)**
Anxiety	79/144 (54.9)
Posttraumatic stress disorder	48/144 (33.3)
Substance use-related disorders and addictive disorders	40/144 (27.8)

Previous treatments

Patients had a median number of 3 (IQR: 2-5) well-conducted line from the beginning of the current episode and started at least 28 days before ESK initiation to the end of the follow-up

63 (31.5%) patients had started and ended at least one neurostimulation therapy before ESK initiation: 23/63 (36.5%) at least one ECT, 35/63 (55.6%) at least one rTMS, and 5/63 (8.8%) at least one TDCS

108 (54.0%) patients had at least one antidepressant (including at least one SSRI in 70 [35.0%] and at least one SNRI in 54 [27.0%] patients), while 45 (22.5%) had an atypical antipsychotic, 27 (13.5%) had an antiepileptic, and 17 (8.5%) had lithium.

Esketamine utilization

Dose increased from the beginning (171 [85.5%] patients with 56mg) to the end (153 [76.5%] patients with 84 mg) of the induction.

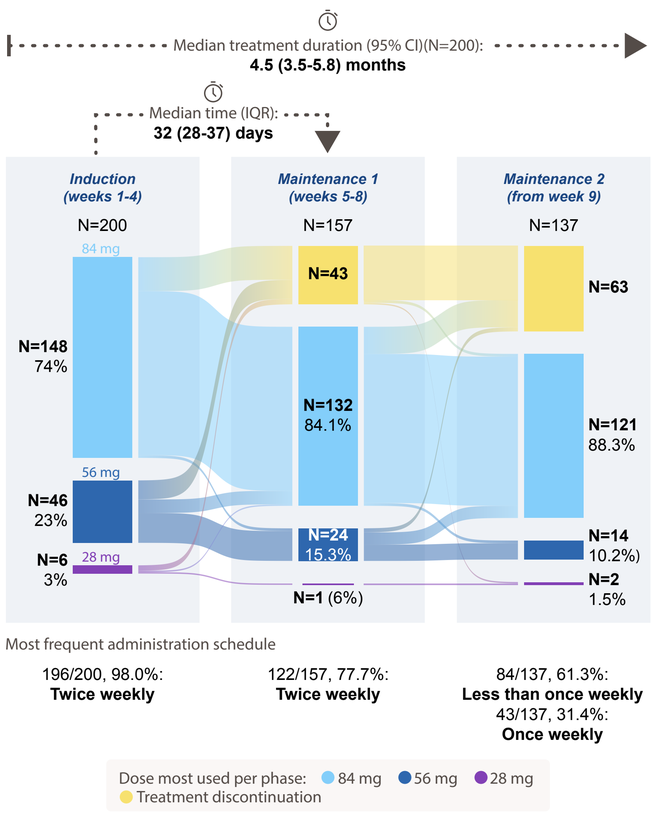

Figure 1. Esketamine most observed posology and administration schedule

A total of 145 (72.5%) patients initiated ESK in a partial hospitalization and/or outpatient context, while the remaining 55 (27.5%) patients initiated ESK during an inpatient hospitalization. 42/55 patients subsequently transitioned to partial hospitalization and/or outpatient treatment after a median duration of 18 days (IQR: 12-41 days).

Esketamine effectiveness

MADRS evolution from baseline

The mean MADRS score in patients still under treatment decreased gradually during follow-up, by -13.0 (95% CI: -14.6;-11.4) points at M1, -15.6 (95% CI: -17.8;-13.3) at M6, and -17.9 (95% CI: -21.6;-14.2) at M12.

The score followed the same decreasing trend in all patients (still treated or not at the considered visit) with MADRS available, and with a sensitivity analysis by imputation of missing MADRS score in all patients.

Figure 2. Mean absolute change in MADRS score

Response and remission

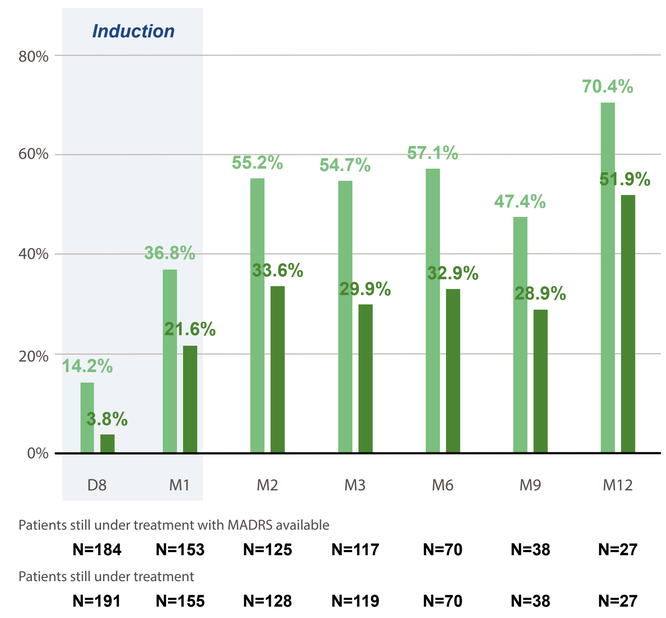

Figure 3. Response and remission in patients still under ESK with MADRS available

Treatment discontinuation

Patients discontinued ESK permanently (n=173) over the 12 months follow-up predominantly for clinical improvement considered as satisfactory (64/173 [37.0%]), for an inadequate response or lack of response during the maintenance (58/173 [33.5%]), after the patient's decision (21/173 [12.1%]), or the occurrence of an adverse event suspected to have a causal relationship with ESK (14/173 [8.1%]).

Safety profile

All patient having received ESK (n=207) were treated for a median (IQR) duration of 4.9 (3.6-5.8) months for the safety analysis.

Table 2. Adverse events

Main Adverse events (Total N=207)	Events (N)	Patients (N, %)
AEs	**1,263**	**136 (65.7)**
AEs related to the treatment	**1,071**	**99 (47.8)**
Dissociation	**465**	**58 (28.0)**
Blood pressure increased	**106**	**24 (11.6)**
Hypertension	**41**	**21 (10.1)**
Serious AEs	**31**	**25 (12.1)**
Serious AEs related to the treatment	**5**	**4**
Headache	**1**	**1 (0.5)**
Serotonin syndrome	**1**	**1 (0.5)**
Bipolar disorder	**1**	**1 (0.5)**
Panic attack	**1**	**1 (0.5)**
Pupils inequal	**1**	**1 (0.5)**