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Research paper

Clinical predictive factors and trajectories of suicidal remission over 6 weeks following intravenous ketamine for suicidal ideation

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ABSTRACT

Background: Ketamine is efficient for short-term reduction of suicidal ideas. Predictive factors and outcome trajectories are poorly characterized.
Methods: Secondary analyses were conducted on the KETIS study (Abbar et al. BMJ 2022): 156 suicidal patients were randomized to two intravenous infusions of racemic ketamine (0.5 mg/kg) or placebo. Response or remission was assessed over six weeks based on the Beck Scale for Suicidal Ideation (SSI). We calculated i) predictive values of 12 baseline variables on remission ii) outcome courses, and iii) positive (PPV) and negative predictive values.
Results: In multivariate analyses, bipolar disorder, lower patient-rated suicidal ideas, and higher physical pain were predictive of suicidal remission at day 3. No clinical factor predicted remission at week 6. Twenty and 24 different clinical courses were identified in early (day 3) and later (week 6) follow-up, respectively, including around 40 % sustained remission, 50 % fluctuating course and 10 % no response. Suicidal remissions at day 1 and day 3 were highly predictive of remissions at day 3 and week 6 (PPV = 96.8 and 92.6 %).
Limitations: SSI may not be adapted for rapid variations and repeated measures.
Conclusions: Clinical factors were poorly predictive of remission. Fluctuations in suicidal ideas were frequent, even after ketamine (although less than placebo), necessitating vigilance and multimodal care. Remission at day 1 after one infusion was highly predictive of future remission. The benefits of a second infusion will have to be tested.

1. Introduction

The 12-month prevalence of suicidal ideation is around 2 % of the general population in the world (Borges et al., 2010), with significant variations between even neighboring countries (Bernal et al., 2007). Of these, 10–50 % will attempt suicide (Borges et al., 2006; Han et al., 2015; Leon et al., 2019). Overall, around 700,000 people globally die from suicide each year (World Health Organization, 2019).

There are limited evidence-based options for the treatment of suicidal crisis (Witt et al., 2019; Lengvenyte et al., 2021; Harmer et al., 2022). For instance, there is no robust demonstration that hospitalization, a widely used crisis intervention, prevents suicide, while it has been shown that suicide rates are high during psychiatric hospitalization and immediately after discharge (Bowers et al., 2010; Chung et al., 2019; Wang et al., 2019b; Jollant et al., 2022). Similarly, benzodiazepines are often used in acute phases of mental disorders in spite of concerns regarding an increased facilitation of suicidal acting-out (Tournier et al., 2023).

In contrast, ketamine can provide a rapid remission of suicidal ideation, within minutes or hours, in many suicidal individuals (Witt et al., 2020; Bahji et al., 2021; Xiong et al., 2021; Jollant et al., 2023), opening new perspectives in the management of suicidal crises. Meta-analyses further suggest a significant difference relative to control drug/placebo for the first 72 h (Witt et al., 2020). In a large clinical trial published using racemic ketamine (KETIS study), two intravenous ketamine infusions provided full remission of suicidal ideas at day three in

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63.0 % of patients as compared to 31.6 % in the placebo group (Abbar et al., 2022). This effect was mainly found in patients with a bipolar disorder as a main diagnosis, but not in patients with a depressive disorder or in other affective disorders. Overall, the effect was maintained at week six post-infusion, although groups were not statistically different due to increasing rates of remission in the placebo group (69.5 % Ketamine vs. 56.3 % Placebo). Of note, a potential mediating effect of psychological pain was found. In this article, we extended these initial analyses with the general objective to provide useful information for clinical practice.

We first aimed to identify baseline clinical factors predicting remission at day three (hereafter named early period) and week six (later period) of ketamine intake, to identify the population most likely to benefit from this treatment. A few studies previously investigated this question. In a meta-analysis of randomized-controlled trials using ketamine, Bahji et al. (Bahji et al., 2021) reported a lack of effect on "suicidality" of depression treatment-resistance, depression type (bipolar/unipolar), or trial design (crossover/parallel). In contrast, there was a significant effect on suicidal ideation when the comparator was active, or when ketamine was given as adjunctive treatment. Wang et al. (Wang et al., 2019a) showed a more rapid effect of ketamine on suicidal ideation when the type of depression was characterized by melancholic-anxious features. Regarding suicidal characteristics at baseline, Price et al. (Price et al., 2014) reported higher change in suicidal ideation in those with higher baseline suicidal scores and those with a personal history of suicide attempt. Ballard et al. (Ballard et al., 2018) found older age, longer duration of depressive episode and a history of sexual abuse to increase the odds of being in remission of suicidal ideas, while suicidal ideation at baseline and a history of self-injury were both associated with lower odds.

Second, we aimed to examine and characterize individual trajectories of response and remission in people who received ketamine. Mean measures of remission at two time points do not accurately reflect the complexity of clinical courses. Ballard et al. (Ballard et al., 2018) previously identified three groups according to clinical outcomes following ketamine intake: non-responders, responders, and remitters with rates at day 3 of 32, 44 and 24 %, respectively.

Finally, we investigated the possibility that very early response to ketamine is predictive of later outcome. Ballard et al. (Ballard et al., 2018) reported that rates of suicidal remission were similar at day one and three, suggesting limited changes in suicidal scores during this narrow early period after the immediate response to ketamine intake. If confirmed, this would have practical implications, notably on the optimal number of ketamine infusions.

The present article aims to improve the description of the effects of ketamine infusion in suicidal patients notably Aim 1) identify baseline clinical factors predictive of suicidal remission during the early (day 1 to day 3) and later (day 3 to week 6) periods; Aim 2) describe the trajectories of suicidal response and remission during both periods. Aim 3) analyze the predictive value of very early remission on later remission. We believe these findings will help clinicians make a valuable use of this drug.

2. Methods

2.1. The KETIS study

We used data collected in the KETIS research project (clinicaltrials.gov: NCT02299440; EudraCT: 2014-001324-30) between 13 April 2015 and 12 March 2019 and previously published (Abbar et al., 2022). Briefly, this was a 6-week randomized-controlled trial comparing two intravenous infusions at 24 h-interval of ketamine (0.5 mg/kg) or placebo. Three groups of patients were a priori recruited according to their main psychiatric diagnosis: bipolar disorders; depressive disorders; and other affective disorders. Patients were all adults, hospitalized voluntarily, with a clinician-rated scale for suicidal ideation (SSI, (Beck et al., 1997)) score $\geq$ 4, with no personal history of psychotic symptoms or schizophrenia or substance dependence over the last month (expect tobacco or cannabis), with a negative urine test screening for illicit drugs, not currently breastfeeding or pregnant, with no major somatic disorder or unstable medical condition, and no contra-indication to ketamine.

In total, 73 patients were randomized to the experimental group, and 83 to the placebo group. Main diagnoses in the ketamine and placebo groups were, respectively: 26/26 with a bipolar disorder (mixed episodes: 1 patient in ketamine and 2 in placebo arm; all others in depressive episode), 26/30 a depressive disorder, and 21/27 another affective disorder; 106 (67.9 %) were females, and the median ages were 38 and 41 (range 18 to 76). 93.1 % of patients in the ketamine group and 85.4 % in the placebo arm had a past history of a suicidal act. Median SSI scores were 22 (16–26) in the ketamine arm and 20 (16–24) in the placebo arm. From baseline to day 3, three patients discontinued follow-up in the placebo group and none in the ketamine group. From day 3 to week 6, 14 discontinued follow-up in the placebo group and 13 in the ketamine group.

The main outcome was the rate of remission of suicidal ideas measured with the SSI at day 3 (i.e., two days after the last infusion). A secondary outcome was the rate of suicidal remission at week 6. At each timepoint, remission was defined as a clinician-rated SSI score $\leq$ 3.

2.2. Current outcomes and statistical analyses

2.2.1. Aim 1

To identify predictive factors of suicidal remission at day 3 and week 6, 12 baseline variables were analyzed: main diagnosis (bipolar disorder, major depressive disorder, other affective disorder); age; sex; body mass index; physical and psychological pain – visual analog scale (PPP-VAS) (Jollant et al., 2019) - current psychological and physical scores; clinician-rated SSI score; patient-rated SSI score; Beck Hopelessness Scale score; Inventory of Depressive Symtoms-30 (IDS-30) score; Clinical Global improvement score; and a personal history of a suicidal act. Each variable was analyzed using univariate logistic regression, and those significant at a threshold of 0.2 were selected in multivariate logistic regression. The final model was obtained after stepwise selection on the Akaike Information Criteria (AIC). Results are given with their Odds Ratio (OR) and 95 % Confidence Interval (95 % CI).

In addition, comparison of baseline variables between patients with a completed SSI score at week 6 and patients with a missing SSI score at week 6 was run in both ketamine and placebo arms by a Fisher's exact test for qualitative variables and a Mann-Whitney Wilcoxon test for quantitative variables.

2.2.2. Aims 2 and 3

To investigate individual trajectories of response and remission, we separately evaluated two periods. The early period corresponding to the first three days during which three timepoints were considered: day 1, 2, and 3. The later period ranged from day 3 to week 6 during which three timepoints were assessed: day 3, week 2, and week 6. At each timepoint and for each patient, remission was defined as a clinician-rated SSI score $\leq$ 3, and response as 50 % or more reduction in clinician-rated SSI score as compared to the baseline value. For each individual at each timepoint, one of the following code was given: 0 = lack of response; 1 = response; 2 = remission. Then, for each period, individual trajectories were defined according to the combination of remission/response/lack of response for each of the three respective timepoints (leading to maximum possible 27 combinations per period).

Aim 3: The positive and negative predictive values of remission at day 1 in terms of remission at day 3, and at day 3 in terms of remission at week 6 were calculated.

Among the 73 patients who received ketamine, trajectory analyses were conducted in 67 patients for the early period, as some SSI measures were missing for 6 patients at some timepoints, and 56 patients for the

later period due to dropouts. Among the 83 patients who received placebo, analyses for each period were conducted in 77 and 59 patients, respectively.

A p value ≤ 0.05 was considered as statistically significant.

Statistical analysis was performed with *R*3.5.1 software (R Development Core Team, (2018). R Foundation for Statistical Computing, Vienna, Austria).

3. Results

There was no significant difference between patients who completed SSI scores at week six and those with missing information on both ketamine and placebo arms ($N = 59$ vs 14, and 64 vs 19, respectively).

3.1. Baseline clinical factors predictive of suicidal remission at day 3

Following univariate analyses of the 12 baseline variables selected (Table 1), we retained four: main diagnosis, baseline patient-rated SSI score, baseline IDS-30 score, and baseline PPP-VAS physical pain score. In multivariate analyses, the following variables were associated with a higher rate of remission under ketamine: a main diagnosis of bipolar disorder, a higher PPP-VAS physical pain score at baseline, and a lower patient-rated SSI score at baseline.

Table 1
Predictive factors of remission at Day 3 in the ketamine arm.

Variables	No remission at Day 3 $n = 27$	Remission at Day 3 $n = 46$	Univariate p-value	Multivariate Odd-Ratio (95%CI)
Diagnosis			0.006	
Bipolar Disorder, N (%) (ref)	4 (15.4 %)	22 (84.6 %)		–
Depressive Disorders, N (%)	15 (57.7 %)	11 (42.3 %)		0.08 (0.01–0.36)
Other affective Disorders, N (%)	8 (38.1 %)	13 (61.9 %)		0.32 (0.07–1.4)
Age, mean (SD)	37.4 (16.6)	41.1 (13.0)	0.3	
Sex (Women), N (%)	21 (77.8 %)	33 (71.7 %)	0.6	
Body Mass Index, mean (SD)	25.1 (6.1)	26.2 (6.0)	0.4	
PPP-VAS psychological pain, mean (SD)	7.3 (2.4)	7.2 (2.0)	0.8	
PPP-VAS physical pain, mean (SD)	2.2 (2.7)	3.4 (3.3)	0.1	1.25 (1.03–1.55)
SSI-score, patient-rated scale, mean (SD)	18.2 (4.9)	15.6 (3.9)	0.01	0.85 (0.72–0.87)
SSI-score, clinician-rated scale, mean (SD)	22.6 (5.6)	20.8 (6.6)	0.2	
BHS score, mean (SD)	15.5 (3.2)	14.4 (3.9)	0.2	
IDSC-30 score, mean (SD)	41.4 (11.0)	36.9 (11.2)	0.1	–
CGI score, mean (SD)	5.7 (0.7)	5.7 (0.7)	0.8	
Previous history of suicide attempts, N (%)	25 (92.6 %)	42 (93.3 %)	0.9	

PPP-VAS: Physical and psychological Pain-Visual Analog Scale; SSI: Beck Scale for Suicidal Ideation; BHS: Beck Hopelessness Scale; IDS-30: Inventory of Depressive Symtoms-30; CGI: Clinical Global Improvement; SD: Standard Deviation; CI: Confidence Interval.

Findings in the placebo arm are reported in Supplementary Table 1. In multivariate analyses, the following variables were associated with a higher rate of remission under placebo: a higher body mass index, and a lower psychological pain.

3.2. Individual remission and response trajectories over the first three days

Individual trajectories in SSI scores in the ketamine arm are presented in Fig. 1 for the early period. See also Supplementary Fig. 1a, b, c for findings by main diagnostic group.

Of note, only one patient showed a limited increase in SSI scores after the first ketamine infusion.

When considering the three SSI measures at day 1, 2 and 3, 20 different courses were found (see details in Table 2). In the ketamine arm, a frequent course was a remission at day 1 that was maintained at day 2 and 3 (41.8 %) This course mainly concerned patients with bipolar disorder as the main diagnosis (64 % in bipolar disorder vs. 21.7 % in depressive disorders and 36.8 % in other affective disorders). It was much lower in the placebo arm (10.4 %). A second group was patients who never responded to ketamine at any of the three timepoints (10.4 %). This mainly concerned patients with depressive disorders (21.7 % vs. 0 % for bipolar disorders and 10.5 % for other affective disorders). This course was more frequent in the placebo arm (33.8 %). Fluctuations in suicidal measures during this period were therefore found in 47.8 % of the ketamine arm and 55.8 % of the placebo arm.

3.3. Predictive value of remission at day 1 on remission at day 3

Among the patients who achieved remission at day 1 (46.3 % of the ketamine arm and 18.2 % of the placebo arm), 96.8 % of patients were in remission at day 3 in the ketamine arm vs. 64.3 % in the placebo arm (representing the remission positive predictive values).

Among the patients who responded to treatment at day 1 but were not in remission (19.4 % of the ketamine arm and 22.1 % of the placebo arm), 61.5 % were in remission at day 3 in the ketamine arm vs. 58.8 % in the placebo arm.

Finally, among the patients who did not respond to treatment at day 1 (34.3 % of the ketamine arm and 59.7 % of the placebo arm), 21.7 % finally reached remission in the ketamine arm vs. 15.2 % in the placebo arm. The remission negative predictive value (the probability not to be in remission at day 3 when there is no remission at day 1) was 78.3 % for ketamine and 84.8 % for placebo.

Patients who achieved remission at day 3 fell into two groups: those with a rapid remission reached by day 1 (69.8 % of day-3-remitters in the ketamine arm vs. 34.6 % in the placebo arm), and those who only reached remission at day 2 or 3, therefore after the second infusion (30.2 % of day-3-remitters in the ketamine arm vs. 65.4 % in the placebo arm). Rapid remission was found in 69.6 % of day-3-remitters in patients with bipolar disorder vs. 50 % for depressive disorders and 81.8 % for other disorders.

3.4. Baseline clinical factors predictive of suicidal remission at week 6

We retained the four following variables from univariate analyses: baseline patient-rated SSI score ($p = 0.1$), gender ($p = 0.1$), baseline BHS score ($p = 0.2$), and main diagnosis ($p = 0.2$). In multivariate analyses, none of these variables reached significance.

3.5. Individual remission and response trajectories between day 3 and week

Individual courses over this later period are presented in Fig. 2. During this period, 24 courses were identified (see Table 3). The most frequent course was a sustained remission over the three timepoints in the ketamine arm (42.9 %). Sustained remission was lower in the

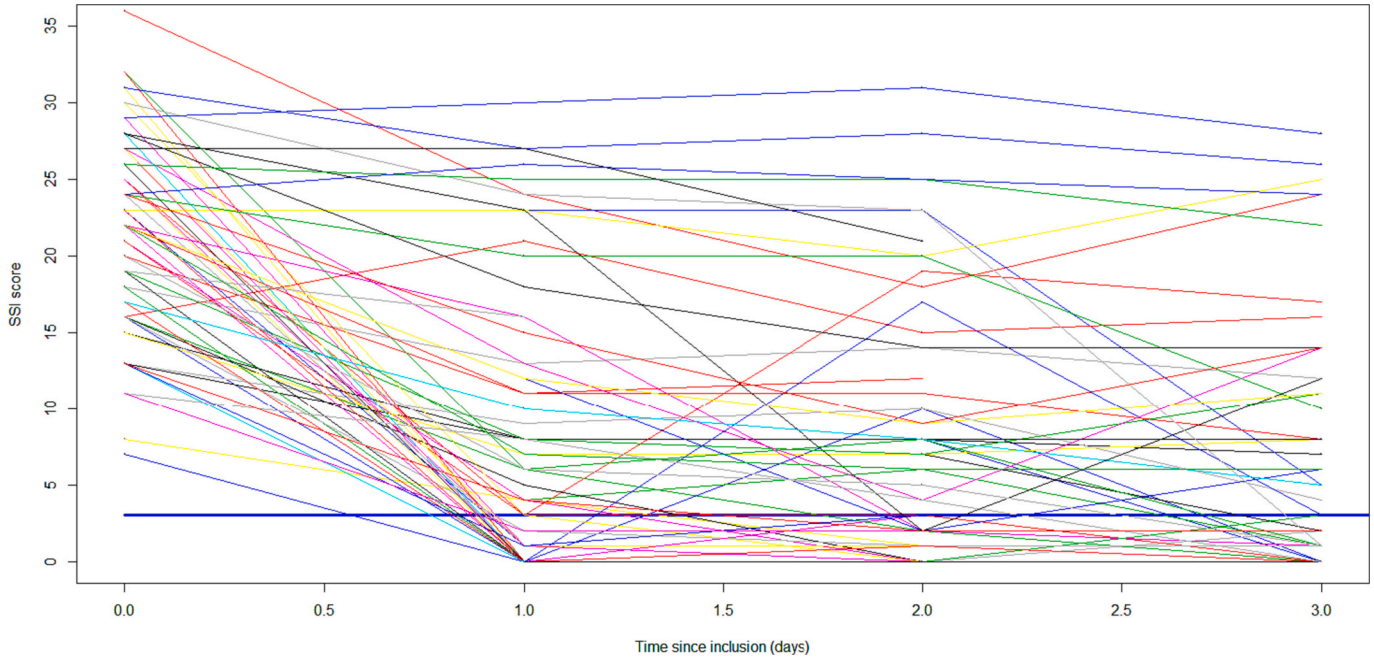

Fig. 1. Individual Beck Scale for Suicidal Ideation (SSI, clinician-rated version) scores at baseline, day 1 (24 h after first infusion), day 2 (24 h after second infusion), and day 3 (main outcome) for each patient in the ketamine arm ($n = 73$).
Each line represents one patient. The bold blue line represents the threshold for remission (≤3). Missing data for a patient at a time point implies a discontinuity in the patient's curve. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Combinations of individual courses in the ketamine and placebo arms based on the clinical status (remission/response/lack of response of suicidal ideation) at each of the three timepoints (day 1, day 2 and day 3) of the early period.

Combinations	Placebo arm (N)	% of patients within arm	Ketamine arm (N)	% of patients within arm
0-0-0	26	33.8	7	10.4
0-0-1	7	9.1	4	6.0
0-0-2	4	5.2	2	3.0
0-1-0	2	2.6	2	3.0
0-1-1	3	3.9	3	4.5
0-1-2	1	1.3	2	3.0
0-2-0	1	1.3	0	0.0
0-2-1	0	0.0	2	3.0
0-2-2	2	2.6	1	1.5
1-0-0	2	2.6	0	0.0
1-0-1	1	1.3	0	0.0
1-1-0	2	2.6	3	4.5
1-1-1	2	2.6	2	3.0
1-1-2	3	3.9	3	4.5
1-2-2	7	9.1	5	7.5
2-0-0	3	3.9	1	1.5
2-0-1	2	2.6	0	0.0
2-0-2	0	0.0	2	3.0
2-2-1	1	1.3	0	0.0
2-2-2	8	10.4	28	41.8

Due to SSI data missing, analyses were conducted in 67 patients in the ketamine arm and 77 patients in the placebo arm. 0 = lack of response; 1 = response; 2 = remission. Remission was defined as a clinician-rated SSI score ≤ 3, and response as 50 % or more reduction in clinician-rated SSI score as compared to the baseline value at inclusion.

placebo arm (18.6 %). A small percentage showed a total lack of response at the three timepoints of the late period: 7.1 % in the ketamine arm and 10.2 % in the placebo arm. Fluctuations in suicidal measures during this later period were therefore found in 50.0 % of the ketamine arm and 71.2 % of the placebo arm.

3.6. Predictive value of remission at day 3 on remission at week 6

Among the patients in full remission at day 3 (58.7 % of the ketamine arm and 26.0 % of the placebo arm), 92.6 % were still in remission at week 6 in the ketamine arm vs. 84.6 % in the placebo arm (remission positive predictive value).

Among the patients who responded at day 3 without being in remission (17.4 % of the ketamine arm and 12.0 % of the placebo arm), 62.5 % were in remission at week 6 vs. 83.3 % in the placebo arm.

Among the patients who did not respond at all at day 3 (23.9 % of the ketamine arm and 62.0 % of the placebo arm), 45.4 % reached remission at week 6 in the ketamine arm vs. 32.3 % in the placebo arm. The remission negative predictive value in the ketamine arm was 63.9 % for ketamine and 73.0 % for placebo.

4. Discussion

In this study, we re-analyzed data from our seminal KETIS study. Previous meta-analyses (Witt et al., 2020) and our own study (Abbar et al., 2022) showed that ketamine outperforms placebo on suicidal response and remission within the first 72 h. Following this early period, no group difference can be found, mainly due to an increasing rate of response/remission in the placebo group. However, this difference between an early (defined here as the period between day 1 to day 3) and a later (here, day 3 to week 6) period seems to be valid when it comes to prediction and individual outcome trajectory.

First, a limited number of clinical factors were predictive of remission at day 3, and none were predictive of 6-week remission. In the short-term, the strongest clinical factor was bipolar disorder. It was more predictive of suicidal remission at day 3 than depressive disorders, however, it did not differ from other affective disorders. This is in disagreement with a meta-analysis by Bahji et al. (Bahji et al., 2021), which found no difference between unipolar and bipolar disorders. This discrepancy could be explained by the small number of bipolar patients, and the over-representation of treatment-resistant bipolar depression in the Bahji et al. study. Our study additionally revealed that two-thirds of

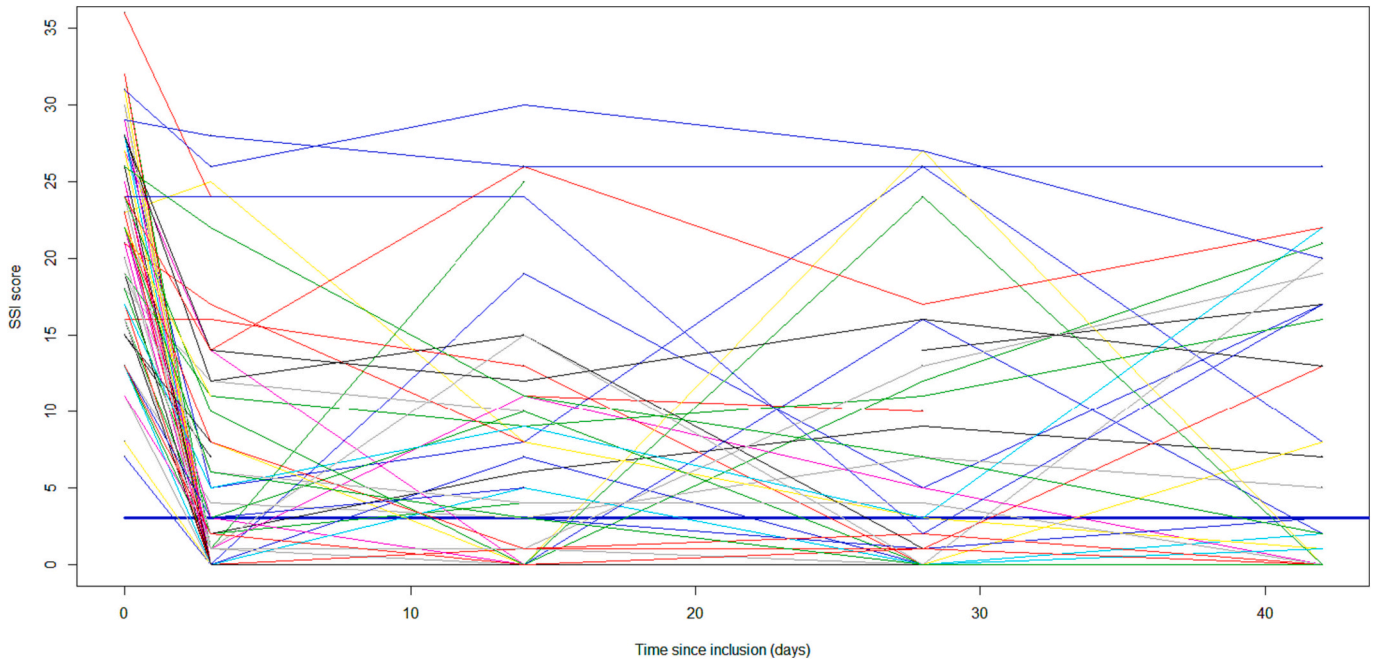

Fig. 2. Individual Beck Scale for Suicidal Ideation (SSI, clinician-rated version) scores at baseline, day 3, week 2, week 4, and week 6 for each patient in the ketamine arm (n = 73).
Each line represents one patient. The bold blue line represents the threshold for remission (≤3). Missing data for a patient at a time point implies a discontinuity in the patient's curve. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Combination of individual courses in the ketamine and placebo arms based on the clinical status (remission/response/lack of response of suicidal ideation) at each of the three timepoints (day 3, week 2 and week 6) of the later period.

Combinations	Placebo arm (N)	% of patients within arm	Ketamine arm (N)	% of patients within arm
0-0-0	6	10.2	4	7.1
0-0-1	5	8.5	0	0
0-0-2	4	6.8	2	3.6
0-1-0	5	8.5	1	1.8
0-1-1	1	1.7	0	0
0-1-2	2	3.4	2	3.6
0-2-0	3	5.1	1	1.8
0-2-1	1	1.7	0	0
0-2-2	4	6.8	1	1.8
1-0-0	1	1.7	1	1.8
1-0-2	3	5.1	1	1.8
1-1-1	0	0	2	3.6
1-1-2	2	3.4	1	1.8
1-2-0	1	1.7	0	0
1-2-1	0	0.0	1	1.8
1-2-2	3	5.1	4	7.1
2-0-0	1	1.7	1	1.8
2-0-1	1	1.7	0	0
2-0-2	0	0	1	1.8
2-1-0	0	0	2	3.6
2-1-2	3	5.1	4	7.1
2-2-0	2	3.4	2	3.6
2-2-1	0	0.0	1	1.8
2-2-2	11	18.6	24	42.9

Due to SSI data missing, analyses were conducted in 56 patients in the ketamine arm and 59 patients in the placebo arm. 0 = lack of response; 1 = response; 2 = remission. Remission was defined as a clinician-rated SSI score ≤ 3, and response as 50 % or more reduction in clinician-rated SSI score as compared to the baseline value at inclusion.

bipolar patients showed an early outcome trajectory marked by a remission by day 1 persisting until day 3 (after the second infusion). This early trajectory was less often found in depressive disorders (21.7 %) and in other affective disorders (36.8 %). Thus, bipolar disorder was not only predictive of remission at day 3, but also characterized by a very early and robust remission following ketamine infusion.

Two additional short-term predictive factors were identified in our study: a lower baseline level of suicidal ideas and a higher baseline level of current physical pain. Regarding the level of suicidal ideas at baseline, findings have been mixed so far. Price et al. (Price et al., 2014) reported higher odds of remission following ketamine while Ballard et al. (Ballard et al., 2018) reported the opposite association. Our finding may seem disappointing. However, it should be noted that the effect size of the association was low suggesting limited clinical utility. It should also be noted that clinician-rated SSI was not significant, suggesting that the patient-rated version should be favored. The finding that higher physical pain was predictive of short-term remission is not surprising considering the analgesic effects of ketamine. Finally, as we previously found a mediating effect of mental pain between ketamine and suicidal ideation reduction (Abbar et al., 2022), it is surprising that mental pain does not emerge as a predictive factor.

Second, we found a large number of individual trajectories in terms of suicidal response and remission, both during the early (n = 20 trajectories) and later (n = 24 trajectories) periods of follow-up. However, three main patterns emerged. The first one was a remission at all three points. This was found in 41.8 % of patients during the early period following ketamine (vs. 10.4 % for placebo), and in 42.9 % of patients during the later period in the ketamine arm (vs. 18.6 % for placebo). Therefore, around 40 % patients experienced an early and sustained remission of suicidal ideas with ketamine. A second pattern was the total lack of response or remission over the three timepoints. This represented 10.4 % of patients under ketamine vs. 33.8 % under placebo during the early period, and 7.1 % vs. 10.2 % during the later period. Overall, one patient in ten in our sample thus never reached response of suicidal ideas after ketamine. Finally, for the population with more fluctuating courses (around 50 %), it should be noted that, while remission rates at week 6 were statistically similar in the ketamine and placebo arms (69.5 vs. 56.3 % in an intent-to-treat analytic approach) (Abbar et al., 2022), rates of fluctuating patterns between day 3 and week 6 were lower after

ketamine than placebo (50.0 vs. 71.2 %, respectively). This suggests that ketamine may reduce the overall odd of fluctuations in suicidal ideas more than placebo. Future studies may use more complex models such as latent class classification approaches to identify trajectories.

A last finding relates to the predictive value of early response. Suicidal remission at day 1 was highly predictive of remission at day 3; and remission at day 3 highly predictive of remission at week 6, with respective remission positive predictive values of 96.8 and 92.6 % for ketamine. Negative predictive values were also high during both the early and later periods, 78.3 % and 63.9 % for ketamine, suggesting that most patients who are not in remission at day 1 or day 3 will not reach remission over the 6-week period. Interestingly, among patients in suicidal remission at day 3, only those in rapid remission at day 1 but not those reaching remission at day 2 or 3 differed from placebo (69.8 vs. 34.6 % were in remission at day 1; 30.2 vs. 65.4 % started being in remission at day 2 or day 3). It therefore seems that, while remission rates differed between ketamine and placebo at day 3 (63.0 vs 21.6 %; (Abbar et al., 2022)), the main specific effect of ketamine occurs during the first 24 h following infusion. After this, the placebo effect (i.e., care provided to the hospitalized patient) may be the main driving force leading to long-term follow-up. It would be interesting to know if similar findings would be observed in outpatient settings with more limited care than in hospitalization. This study unfortunately cannot either clarify if a second infusion at 24 h would be beneficial in those not in full remission at day 1.

Although this study had from several strengths (relatively large sample size, 6-week follow-up, a priori defined sub-group of patients with affective disorders), several limitations have to be underlined. First, the sample size was not a priori powered to run complex prediction models. We therefore limited our predictive analyzes to simple regression models and did not run any interactions. Second, the main outcome is suicidal ideation based on the Beck SSI clinician-rated questionnaire. The global score was used, limiting our capacity to investigate finer effects about suicidal cognition. Also, the SSI does not allow a fine characterization of fluctuations, sometime within days, observed during a suicidal crisis. Future studies may use new techniques such as Ecological Momentary Assessment (EMA). Furthermore, to our best knowledge, SSI has not been validated for repeated measures over a very short period of times (e.g., hours or days). Third, as for all studies using ketamine, a limitation is the quality of blinding as ketamine may lead to very recognizable side effects, notably depersonalization. As discussed in the seminal paper, this side effect was however infrequent. We do not know if patients guessed the treatment as this was not measured here. Fourth, treatment could be changed over the 6-week follow-up period, which may have contributed to variations in symptomatology including suicidal ideas. Finally, our protocol used two infusions. It is therefore difficult to assess the potential benefits of such a protocol vs. most protocols using one infusion.

In conclusion, findings from these new analyses of the KETIS study add novel and more nuanced information to our knowledge on ketamine for the treatment of suicidal ideation in patients suffering from an affective disorder. This information may be useful for clinicians as well as for researchers. First, studied clinical factors were poorly predictive of remission and should not lead to patients' selection. Second, various outcome trajectories were observed during the early and later periods. Globally, around 40 % of patients showed an early and sustained remission following ketamine while 50 % showed a more fluctuating pattern, and 10 % a sustained lack of remission. Future randomized-controlled trials should determine if a second infusion at 24 h may be beneficial for the patients not in remission or if benefits are marginal. Moreover, clinicians should remain vigilant and not over-rely solely on ketamine in suicidal patients. Notably, use of ketamine should not replace other preventative measures, as our study also showed that the specific effects of ketamine may be particularly important during the first 24 h, but much less important as compared to placebo effects (i.e., all other cares) afterward. In addition, there is no demonstration to date of a preventative effect of ketamine on suicidal acts. Comparison of ketamine with other demonstrated interventions in suicidal patients such as ECT will also have to be conducted. Finally, the long-term risks of ketamine, including abuse, in this population will have to be further examined.

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CRediT authorship contribution statement

MA conceived the study. MA and PF designed the study and wrote the protocol. FJ conceived these secondary analyses. CD performed the analyses. FJ wrote the first draft. All authors agreed on the final version.

Declaration of competing interest

MA declares fees from Astra Zeneca and Lundbeck, and has been invited to congresses by Janssen-Cilag, Otsuka, Lundbeck, Servier, and Astra Zeneca. All other authors declare no conflict of interest.

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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.2023.11.043.

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