



Ketamine for refractory chronic pain: a 1-year follow-up study

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Abstract

Ketamine is often used in pain clinics for refractory chronic pain, but its long-term efficacy is poorly reported. The main objective was to assess the long-term effect of ketamine on pain and health variables in patients with refractory chronic pain. A prospective, multicenter, 1-year follow-up observational study (NCT03319238) was conducted in 30 French pain clinics where ketamine is commonly prescribed. This study focused on patients with 1 ketamine delivery procedure ($n = 256$). The primary endpoint was pain intensity (0–10 numerical pain rating scale) before and after ketamine every month for 1 year. Secondary outcomes aimed to identify pain trajectories by semiparametric mixture models and to collect adverse events. The following data were obtained for 256 patients: Pain intensity decreased significantly (6.8 ± 1.8 , $n = 240$ at baseline vs 5.7 ± 1.8 , $n = 93$ at 12 months; $P < 0.001$). The effect size of the main endpoint was 0.61 (95% confidence interval: [0.40–0.80]; $P < 0.001$). Three pain trajectories were identified: 16.0% of patients in “mild pain” (mostly neuropathic pain), 35.3% in “moderate pain,” and 45.7% in “severe pain” (mostly fibromyalgia) trajectory. Neuropathic pain and fibromyalgia presented opposite outcomes, pain severity being associated with anxiety, depression, and a poorer quality of life. Adverse events occurred at 1 week in 108/218 [50%] patients, and this rate gradually decreased throughout the follow-up. This real-life study in chronic pain identified distinct pain trajectories and predictive variables of ketamine efficacy. It is now pivotal to further study and optimize the subtyping of patients to provide the most effective and safe ketamine treatment in this vulnerable population.

Keywords: Refractory chronic pain, Ketamine, Pain trajectories

1. Introduction

Chronic pain, defined as pain lasting for more than 3 months,³⁹ affects 27.2% to 32.7% of the general population in France.⁹ Recently, the term “chronic pain” has been considered as a “parent code” for 7 other chronic pain conditions, including chronic primary pain (fibromyalgia and complex regional pain syndrome [CRPS]) and chronic neuropathic pain.⁴⁰

Therapeutic management of chronic pain, especially neuropathic pain and fibromyalgia, is based on antidepressants, antiepileptics, and opioids. Despite the use of this therapeutic arsenal, more than 60% of patients show no improvement or a poor response and often experience adverse effects.^{15,17} This situation suggests the use of other pharmacological

approaches,¹⁸ such as *N*-methyl-D-aspartate receptor antagonists. Indeed, many experimental^{24,25} and clinical studies^{21,43} have shown that the blockade of *N*-methyl-D-aspartate receptor with antagonists such as ketamine could improve chronic pain.²⁸

Ketamine, an anesthetic agent, provides powerful analgesia and amnesia.²⁰ Ketamine efficacy has been reported in patients with refractory chronic pain at subanesthetic doses⁴ and in phantom limb pain,³⁵ postherpetic neuropathic pain,¹⁶ and CRPS.^{33,34} Ketamine is commonly used in pain clinics for the management of chronic pain, but the efficacy of ketamine remains controversial in the literature on the short term,^{12,32} and no study has followed patients beyond 3 months.³³

The main objective of this observational study was to assess the ketamine effect on pain in patients with refractory chronic pain over 1 year. Other objectives aimed to identify pain trajectories, to characterize related demographic and clinical variables, and to collect adverse events and concomitant treatments.

2. Methods

2.1. Study design

This prospective, multicenter, and observational study was conducted in 30 French pain clinics (Observational Ketamine And Pain study Consortium). All included patients were followed up with phone calls over 1 year by the Clinical Research Center/Clinical Investigation Center Inserm 1405, Clermont-Ferrand University Hospital, France. This study was approved by the Ethics Committee (CCTIRS, CNIL, and CPP Sud-Est, France) and registered on clinicaltrials.gov (NCT03319238).

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 163 (2022) 690–701

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<http://dx.doi.org/10.1097/j.pain.0000000000002403>

2.2. Study population

Male and female patients older than 18 years, with chronic pain for more than 6 months (peripheral or central neuropathic pain, fibromyalgia, CRPS, or other chronic pain) and who required ketamine in their pain care pathway, were included.

Patients were recruited in the pain clinic where they were usually taken in charge. The clinician evaluated the eligibility criteria, explained the objectives of the study, and gave an information and nonopposition form. The investigator specified to the patient that he/she could refuse to participate to the study. This study in 256 patients with only 1 ketamine delivery procedure is part of a larger study with 585 receiving various ketamine dosages, routes of administration, and in-patient duration.

2.3. Study drug and administration

As there is so far no consensus on ketamine use in chronic pain, ketamine delivery procedures in pain clinics vary in terms of dosage, duration, frequency, number, and route of administration (eg, a single dose of 0.2 mg/kg over 40 minutes or 0.1 mg/kg/day once a week for 8 weeks, intravenous or subcutaneous). Every pain clinic followed its own protocol. For clarity sake, we used cumulative doses in milligrams (total dose of ketamine received over the duration of each procedure) and cumulative days (number of days during each ketamine procedure). For example, a dose of 0.5 mg/kg/day administered once a month for 3 months was equivalent to a cumulative dose of 105 mg for a 70-kg person.

2.4. Follow-up procedures

At inclusion and before ketamine administration, a form was completed to collect baseline data: demographic information, ketamine-naïve status and delivery procedure, pain and its characteristics, and concomitant analgesic treatments and questionnaires. A first phone call was given 1 week after ketamine delivery procedure. Then, patients were followed up for 1 year by a monthly phone call to collect longitudinal data: pain assessment intensity, questionnaires, concomitant drug and nondrug treatments, and adverse events.

2.5. Study objectives and endpoints

The main objective was to evaluate pain relief with ketamine over a 1-year period, and the endpoint assessed the average pain intensity after ketamine over 1 year with the numerical pain rating scale ranging from 0 = no pain to 10 = maximal tolerable pain.

Secondary objectives and endpoints were to identify longitudinal pain trajectories with semiparametric mixture models to characterize the pool of patients belonging to each pain trajectory by demographic data (sex, age, number of concomitant analgesic treatments, ketamine-naïve status, and type of pain), pain intensity (numeric pain rating scale), and questionnaires at baseline (anxiety, depression by the Hospital Anxiety and Depression Scale,⁴⁴ and quality of life by the 12-item Short-Form survey⁴²). Other objectives were to report ketamine delivery procedures used in pain clinics (dose, frequency, route of administration, and duration) to collect adverse events and concomitant drug and nondrug treatments.

2.6. Sample size

Sample size estimation was determined sequentially according to rules-of-thumb for determining the minimum number of subjects required to Cohen's recommendations¹¹ who has defined effect-

size bounds as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$, "grossly perceptible and therefore large"), with effect size can be seen as the quantitative measure of the magnitude of difference and calculated as the difference between 2 mean values divided by SD. So, with 97 patients evaluated at baseline and 12 months, an effect size greater than 0.5 (ie, 1-point difference for an SD at 2) can be highlighted for numerical pain rating scale change, with a two-sided type I error at 0.001 (correction because of multiple comparisons), a statistical power at 95%, and an intraindividual correlation coefficient equals 0.5.

2.7. Statistical analysis

Statistical analyses were performed using Stata software, Version 15 (StataCorp, College Station, TX). All tests were two-sided, with a type I error set at 5%. Continuous data were expressed as mean $\pm$ SD or median [interquartile range] according to statistical distribution. The assumption of normality was assessed by using the Shapiro-Wilk test. To analyze longitudinal data, random-effects models for repeated data were performed, with time as fixed effect and patient as random effect to take into account between- and within-patient variability. To compare changes between groups, group $\times$ time-point evaluation interaction was studied. A Sidak's type I error correction was applied to perform multiple comparisons. For continuous endpoints, the normality of residuals was studied using the Shapiro-Wilk test. When appropriate, a logarithmic transformation was proposed to achieve the normality of dependent outcome. The results were expressed as effect sizes (d) and 95% confidence intervals (CIs) and were interpreted according to Cohen's recommendations aforementioned. To measure the evolution of binary variable such as treatment changes, the McNemar test with exact P -value for paired proportions was applied.

Then, to identify distinctive trajectories of pain, semiparametric mixture models (group-based trajectory model noted GBTM) were performed to model the relationship between pain and time, for each trajectory, the shape of the trajectory, and the estimated proportion of the population belonging to each trajectory. These probabilities are called the posterior probability of group membership. To create the profiles, individuals were assigned to the trajectory group to which they most likely belonged based on their measured history of pain. Groupings may identify distinct subpopulations. The analysis provides a formal way to determine the best-fit number of trajectories and a precision estimate of group membership allocation which can be expressed using observed probabilities and posteriori probabilities. Nagin lays out several statistically oriented criteria for assessing model adequacy.²⁷ These include (1) obtaining for each trajectory group a close correspondence between the estimated probability of group membership and the proportion assigned to that group based on the posterior probability of group membership, (2) ensuring that the average of the posterior probabilities of group membership for individuals assigned to each group exceeds a minimum threshold of 0.7, (3) establishing that the odds of correct classification based on the posterior probabilities of group membership exceed a minimum threshold of 5, and (4) observing reasonably tight CIs around estimated group membership probabilities. Furthermore, the best-fitting model will be selected according to the Bayesian information criterion.

Sensitivity analyses were performed to evaluate the statistical nature of missing data and their possible impact on results. According to this analysis, we considered the missing data differently depending on whether they were during the follow-up or for patients who were lost to follow-up. In situations where data are missing at random, maximum likelihood estimations will provide parameter estimates that are asymptotically unbiased. When data are missing

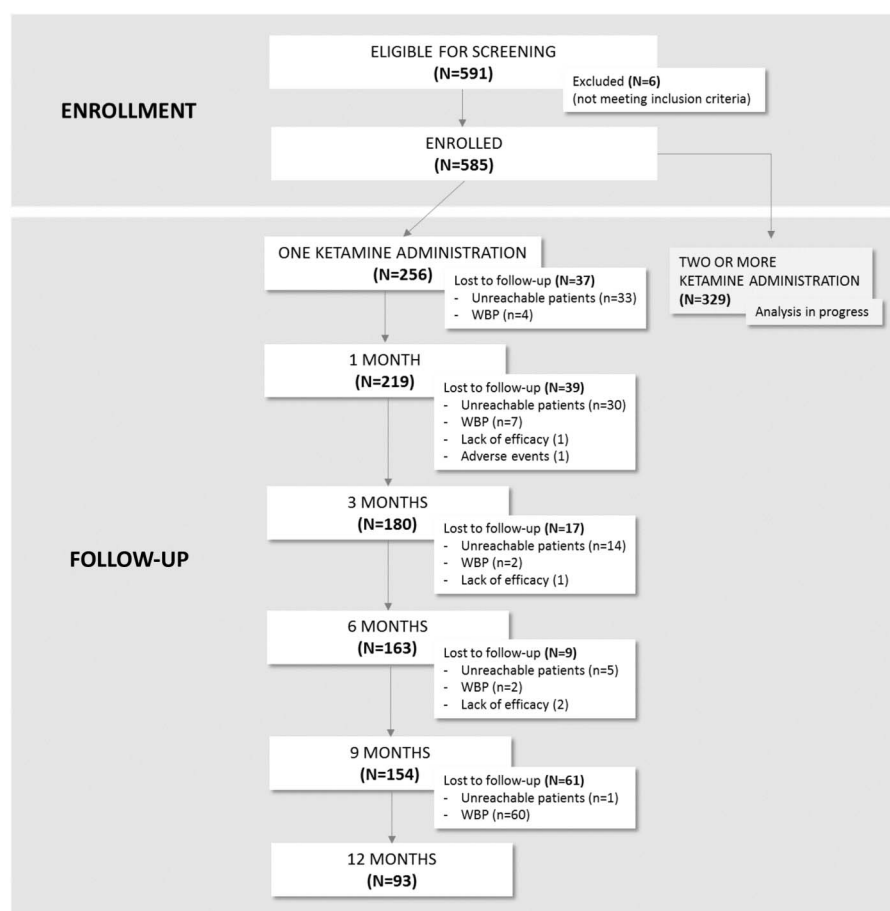


Figure 1. Flowchart of the study. WBP, withdrawal by patient. WBP, withdrawal by patient.

at random, information from the data set can, in addition, be used to impute missing data before input into the trajectory model.²⁶ Accordingly, only missing data during the follow-up have been imputed using the LOCF procedure, and missing data after the last contact were not replaced. As all patients have at least 2 pain points, this analysis was conducted on sample of all patients ($n = 256$). A comparison of patients' characteristics between participants who remained in the entire study and others was also conducted.

The continuous variables were then compared between independent trajectory groups by analysis of variance (ANOVA) or the Kruskal–Wallis test if the assumptions of ANOVA were not met. The homoscedasticity was analyzed using the Bartlett test. When appropriate (omnibus P -value less than 0.05), post hoc tests were performed taking into account multiple comparisons (Tukey–Kramer after ANOVA and Dunn after Kruskal–Wallis). The comparisons between independent trajectories were performed using χ^2 or Fisher exact tests for categorical variables. When appropriate (omnibus P -value less than 0.05), a Marascuilo post hoc procedure was performed.^{22,37} However, as Marascuilo procedure can be considered too conservative, Holm–Bonferroni method was also applied to check the results. With only 3 modalities (for comparisons between trajectories groups), the Marascuilo procedure did not underestimate differences between groups, and the results between the 2 approaches were similar.

To determine the parameters associated to pain trajectories, multivariable analyses (ie, multinomial polytomous logistic regression) were performed using stepwise approach (backward and forward) on covariates fixed according to univariate results and to clinical relevance.

A particular attention has been paid to the study of multicollinearity and interactions between covariates (1) studying the relationships between the covariates and (2) evaluating the impact to add or delete variables on multivariable model. Accordingly, 2 multivariable models were described: one including age, sex, and pain with neuropathic characteristics and another including anxiety score, depression score, and the 12-item Short-Form health survey physical score in addition to age, sex, and pain with neuropathic characteristics. Results were expressed as relative risks (RRs) and 95% CI.

3. Results

3.1. Participants

The Observational Ketamine And Pain study was performed from July 7, 2016, to September 21, 2017, and 591 patients were screened among which 585 were included following eligibility criteria. The present analysis focused on 256 of these patients who received only 1 ketamine infusion. On the year of follow-up, 104 patients were lost to follow-up with 79.8% unreachable patient, 15.4% patient withdrawals, 3.8% for lack of efficacy, and 1.0% for adverse events (Fig. 1).

3.2. Demographics, pain profile, and ketamine administration

Characteristics at baseline of the included sample are presented in Table 1 (see Table, patients were 50.7 ± 11.5 years and were mainly

Table 1**Demographics and clinical characteristics of patients with chronic pain at baseline before ketamine administration.**

Characteristics	Initial baseline		Mean (SD)
	N	Number (%)	
Demographics			
Age (y)	256	—	50.7 (11.5)
Sex (female)		194 (75.8)	—
Patient history			
Neurological/Psychological disorder	256	64 (25.0)	—
Gastrointestinal disease		36 (14.1)	—
Heart disease		42 (16.4)	—
Migraine		28 (10.9)	—
Lung disorder		14 (5.5)	—
Thyroid disorder		16 (6.3)	—
Diabetes		12 (4.7)	—
Cancer		8 (3.1)	—
Ear, nose, and throat disorder		7 (2.7)	—
Psoriasis eczema		6 (2.3)	—
Liver disease		3 (1.2)	—
Peripheral vessel disease		3 (1.2)	—
Prostate disorder		1 (0.4)	—
Chronic kidney disease		1 (0.4)	—
None		37 (14.5)	—
Pain-related			
Pain type			
Fibromyalgia	256	115 (44.9)	—
Peripheral neuropathic pain		72 (28.1)	—
Central neuropathic pain		19 (7.4)	—
Complex regional pain syndrome		29 (11.3)	—
Back pain, sciatica, cruralgia, neuralgia, pelvic pain, and gonarthrosis		16 (6.3)	—
Polyarthritis and spondylitis		1 (0.4)	—
Others		5 (2.0)	—
Pain status			
DN4*	125	—	5.2 (2.3)
Score DN4 ≥ 4		99 (79.2)	—
Average pain intensity	240	—	6.8 (1.8)
Average pain < 3		6 (2.5)	—
Average pain [3-6]		91 (37.9)	—
Average pain ≥ 7		143 (59.6)	—
Number of painful peaks (median [IQR])	141	—	4 [2.5; 7.0]
Maximal pain intensity	244	—	8.2 (1.6)
Maximal pain < 3		3 (1.2)	—
Maximal pain [3-6]		23 (9.4)	—
Maximal pain ≥ 7		218 (89.3)	—
Ketamine			
Patient profile (naive)	256	126 (49.2)	—
Administration (after baseline)			
Intravenous route	256	227 (88.7)	—
Cumulative dose (mg)	227		207.2 (115.3)
≤ 100		47 (20.7)	—
100-222		88 (38.8)	—
222-270		61 (26.9)	—
≥ 270		31 (13.7)	—
Duration (d)	227		4.0 (2.2)
1 d		21 (9.3)	—
2 d		2 (0.9)	—
3 d		96 (42.3)	—
4 d		27 (11.9)	—
5 d		69 (30.4)	—
≥ 6 d		12 (5.3)	—

(continued on next page)

Table 1 (continued)

Characteristics	Initial baseline		Mean (SD)
	N	Number (%)	
Emotional aspects			
HAD, anxiety symptoms score	241	—	10.2 (4.4)
Score ≤ 7		73 (30.3)	
Score [8–10]		57 (23.7)	
Score ≥ 11		111 (46.1)	
HAD, depression symptoms score	237	—	9.2 (4.5)
Score ≤ 7		95 (40.1)	—
Score [8–10]		53 (22.4)	—
Score ≥ 11		89 (37.6)	—
Quality of life			
SF-12—physical score	219	—	30.1 (7.5)
SF-12—mental score		—	38.5 (10.7)
Concomitant drugs			
Paracetamol/NSAIDs	245	104 (42.5)	—
Opioids step 2†, nefopam		109 (44.5)	—
Opioids step 3‡		35 (14.3)	—
Antidepressants		146 (59.6)	—
Antiepileptics		68 (27.7)	—
Adjuvants		51 (20.8)	—
Hypnotics/sedatives		37 (15.1)	—
Anxiolytics		59 (24.1)	—
Antipsychotics		13 (5.3)	—
Others		16 (6.5)	—
None		19 (7.8)	—

Data are expressed as mean $\pm$ SD, as median [interquartile range] and as effective (percentages).

* DN4: except for fibromyalgia.

† Opioids step 2: dihydrocodeine; ibuprofen-codeine; paracetamol-codeine; paracetamol-opium; paracetamol-opium-caffeine; paracetamol-tramadol; tramadol; and tramadol-dexketoprofen.

‡ Opioids step 3: morphine; oxycodone; fentanyl; and buprenorphine.

DN4, Douleur neuropathique 4; HAD, Hospital Anxiety and Depression Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; IQR, interquartile range; SF-12, 12-item Short-Form health survey.

women [75.8%]). Regarding the main pain type, 44.5% presented with fibromyalgia, 28.1% presented with peripheral neuropathic pain, and 11.3% presented with CRPS. This population used several concomitant treatments such as antidepressants (59.6% used at least 1), opioids step 2 of the WHO classification⁷ (44.5%), paracetamol/NSAIDs (42.5%), antiepileptics (27.7%), and anxiolytics (24.1%). Seventy-nine percent of patients described neuropathic pain with a DN4 score ≥ 4 . Before ketamine administration, patients had an average pain intensity of 6.8 ± 1.8 , a median of painful peaks of 4 [IQR: 2.5; 7.0], and a maximal pain of 8.2 ± 1.6 .

Most patients received ketamine through the intravenous route (227/256). More than half of them have a cumulative dose of 100 to 222 mg (38.8%, 88/227) or 222 to 270 mg (26.9%, 61/227). The duration of administration of ketamine was 3 days (42.3%, 96/227), 4 days (11.9%, 27/227), or 5 days (30.4%, 69/227) (Table 1).

Supplemental Digital Content 1 (available at <http://links.lww.com/PAIN/B429>) illustrates baseline characteristics of patients lost to follow-up compared with patients with data. Both populations do not differ in most of their initial characteristics (age, sex, main pain type, pain status, ketamine-naïve status, anxiety, quality of life, and concomitant drugs) except for cumulative dose ≤ 222 mg (41.9% patients with data vs 70.2% patients lost to follow-up, $P < 0.001$).

3.3. Global evolution

3.3.1. Pain

The mean numerical pain rating scale score decreased from 6.8 ± 1.8 at baseline ($n = 240$) to 5.7 ± 1.9 one week after ketamine ($n = 256$), 5.7 ± 2.0 at 6 months ($n = 167$), and 5.7 ± 1.8 at 12 months with the last observation carried forward method ($P < 0.001$) (Fig. 2A and Table, Supplemental Digital Content 2,

available at <http://links.lww.com/PAIN/B429>, that illustrates pain evolution depending on LOCF method). The effect size of the main endpoint (12 months vs baseline) was 0.61 (95% CI [0.40–0.80]; $P < 0.001$).

3.3.2. Emotional aspects and quality of life

Concerning the anxiety subscale of HAD, patients presented at baseline a mean score of 10.2 ± 4.4 pointing “doubtful cases” of anxiety. When scores were considered by range, 46.1% (111/214) of patients presented a score ≥ 11 and were considered as “definite cases” of anxiety (Table 1). The anxiety score decreased over time from 10.2 ± 4.4 at baseline ($n = 241$) to 9.4 ± 4.4 one week after ketamine ($n = 254$), 8.3 ± 4.5 at 6 months ($n = 167$), and 8.1 ± 4.3 at 12 months ($n = 93$) with the last observation carry forward method ($P < 0.001$) (Fig. 2B1).

Concerning the depression subscale of HAD, patients presented at baseline a mean score of 9.2 ± 4.5 describing “doubtful cases” of depression. When scores were considered by range, 37.6% (89/214) of patients presented a score ≥ 11 and were considered as “definite cases” of depression while 40.1% (95/214) of patients presented a score ≤ 7 (Table 1). The depression score decreased over time from 9.2 ± 4.5 at baseline ($n = 241$) to 8.3 ± 4.6 one week after ketamine ($n = 252$), 7.5 ± 4.4 at 6 months ($n = 167$), and 7.2 ± 4.7 at 12 months ($n = 93$) with the last observation carry forward method ($P < 0.001$) (Fig. 2B2).

At baseline, the mental health dimension of SF-12 showed a mean score of 38.5 ± 10.7 that increased to 41.6 ± 11.7 at 12 months ($P < 0.001$) (Fig. 2C). There was no difference about physical dimension (baseline vs M12, 30.1 ± 7.5 vs 29.9 ± 9.3 , $P = \text{NS}$).

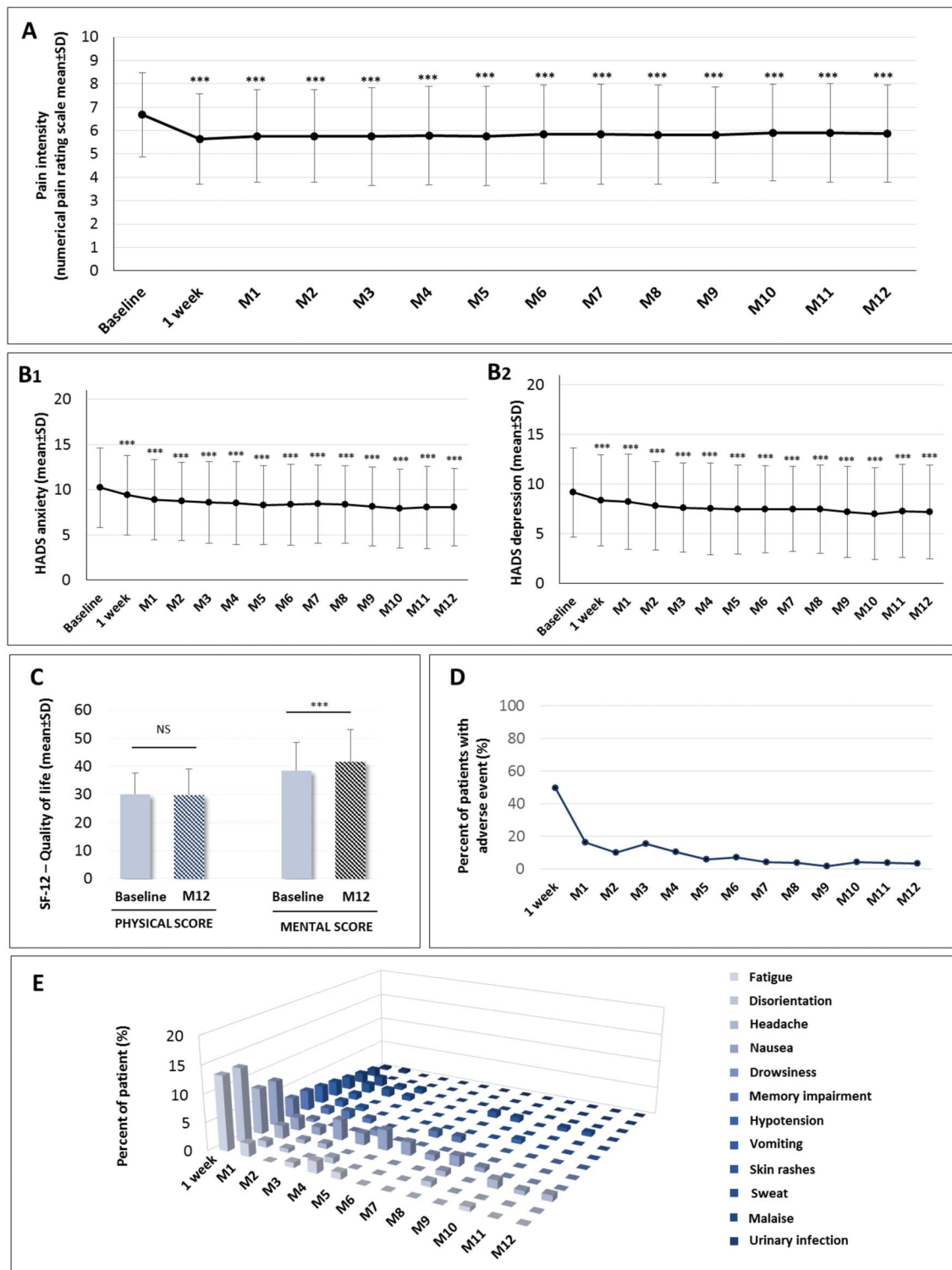


Figure 2. Global evolution. (A) Evolution of mean pain intensity (numerical pain rating scale score). The effect size of the main endpoint (12 months vs baseline) was 0.61 (95% CI [0.40-0.80]; $P < 0.001$). (B1) Evolution of mean anxiety score (by the Hospital Anxiety and Depression Scale). (B2) Evolution of mean depression score (by the Hospital Anxiety and Depression Scale). (C) Score of quality of life 12 months vs baseline (by the 12-item Short-Form survey). (D) Proportion of patients with at least 1 adverse event after ketamine administration during the year of follow-up. (E) Type of adverse events occurring during the patient follow-up. *** $P < 0.001$ (comparison vs baseline). CI, confidence interval; NS, non significant.

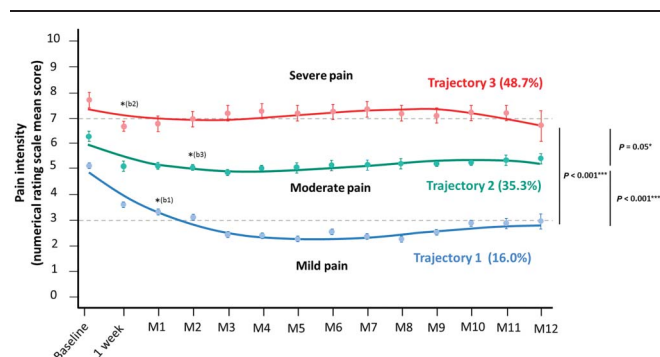


Figure 3. Pain trajectories. One-year pain trajectories after ketamine. Semiparametric mixture models (group-based trajectory model) were performed to model the relationship between pain and time, for each trajectory, the shape of the trajectory, and the estimated proportion of the population belonging to each trajectory. Trajectory 1 corresponds to patients with “mild pain,” trajectory 2 to patients with “moderate pain,” and trajectory 3 to patients with “severe pain.” ^aOmnibus trajectory $\times$ time P -value; ^bintergroup analysis (comparison vs baseline) with b1 corresponds to trajectory 1 vs trajectory 2, b2 corresponds to trajectory 1 vs trajectory 3, and b3 corresponds to trajectory 2 vs trajectory 3; *** $P < 0.001$, ** $P < 0.01$, and * $P < 0.05$.

3.3.3. Safety

After 1 week, 50% (108/218) patients experienced at least 1 adverse event; this rate diminished to 16% (28/172) at 1 month and gradually decreased throughout the follow-up (**Fig. 2D**). The main adverse events were fatigue (13%, 29/218), disorientation (13%, 29/218), headache (8%, 18/218), and nausea (8%, 18/218) at 1 week (**Fig. 2E**).

3.3.4. Concomitant treatments and other approaches

Concomitant treatments were not changed during the follow-up (see Figure, Supplemental Digital Content 3, available at <http://links.lww.com/PAIN/B429>, that describes evolution of concomitant treatment). Most patients had physiotherapy or mild physical activity during follow-up (see Figure, Supplemental Digital Content 4, available at <http://links.lww.com/PAIN/B429>, that illustrates the evolution of nonpharmacological approaches).

4. Pain trajectories

4.1. Identification

After having applied the group-based trajectory model approach to $n = 256$, 3 pain trajectories were identified (**Fig. 3**): 16.0% of patients were in trajectory 1, 35.3% in trajectory 2, and 48.7% in trajectory 3 (observed probabilities), with posterior probabilities equal, respectively, to 16.0%, 35.3%, and 49.6%, average posterior probabilities to 93.8%, 93.7%, and 94.9% (expected $>70\%$), and odds of correct classification based on the posterior probabilities of group membership equal to 77, 28.9, and 19 (expected >5).

Trajectory 1 represented patients with a pain intensity of 5.1 ± 1.9 at baseline (“mild pain”), trajectory 2 with 6.2 ± 1.6 (“moderate pain”), and trajectory 3 with 7.7 ± 1.3 (“severe pain”).

There was a significant interaction between trajectories and time (“mild pain trajectory” vs “moderate pain trajectory,” $P < 0.001$; “mild pain trajectory” vs “severe pain trajectory,” $P < 0.001$; and “moderate pain trajectory” vs “severe pain trajectory,” $P < 0.05$). As shown in **Figure 3**, the mild pain group started around 1 unit below the moderate pain group, then dropped in pain level substantially and by M3 was 2 units lower, a difference that was maintained until the end. Compared with the severe pain

group, the mild pain trajectory also showed a substantially greater difference at time points after the first few.

The time point at which the variation from baseline started to be significantly different between the trajectories was at 1 week, between “mild pain trajectory” and “severe pain trajectory” ($P = 0.039$), at 1 month between “mild pain trajectory” and “moderate pain trajectory” ($P = 0.027$), and at 2 months between “moderate pain trajectory” and “severe pain trajectory” ($P = 0.026$). These results are presented in **Figure 3**.

Furthermore, an analysis on ketamine responders has been realized and showed a statistical difference in 30% (R30%) and 50% (R50%) pain intensity reduction from baseline to 1 week, between patients with “mild pain” and patients with “severe pain” (R30%, 44.7% vs 15.1%, $P < 0.05$; R50%, 31.6% vs 6.7%, $P < 0.05$, respectively). This difference is accentuated at 1 month between patients with “mild pain” and patients with “severe pain” (R30%, 65.6% vs 11.5%, $P < 0.05$; R50%, 43.8% vs 2.1%, $P < 0.05$, respectively), becomes statistically significant between patients with “mild pain” and patients with “moderate pain” (R30%, 65.6% vs 28.2%, $P = 0.05$; R50%, 43.8% vs 11.5%, $P < 0.05$), and presents a reduction of 30% pain intensity between patients with “moderate pain” and patients with “severe pain” (R30%, 28.2% vs 11.5%, $P < 0.05$).

Finally, ketamine-naïve patients and concomitant treatments do not differ between trajectories at baseline (**Table 2**) and over time.

Aforementioned sensitivity analyses highlighted similar results. More precisely, when LOCF procedure was applied for all missing data including lost to follow-up patients ($n = 256$) and when group-based trajectory model analysis was applied only for patient with at least 2 pain evaluations in the survey and without any LOCF procedure ($n = 220$), 3 pain trajectories were also identified with, respectively, the following estimated proportion of the population belonging to each trajectory: 16.9% and 14.4% of patients were in trajectory 1, 41.3% and 41.9% in trajectory 2, and 41.8% and 43.7% in trajectory 3 (see Figure, Supplemental Digital Content 5 and 6, available at <http://links.lww.com/PAIN/B429>).

4.2. Characterization

The demographic/clinical characteristics, pain/emotional status, and quality of life in the trajectories are described in **Table 2** (see Table, Supplemental Digital Content 7, available at <http://links.lww.com/PAIN/B429>, that describes baseline characteristics of 256 patients stratified by trajectory with LOCF method and Table, Supplemental Digital Content 8, available at <http://links.lww.com/PAIN/B429>, that illustrates initial baseline characteristics of 220 patients stratified by trajectory without imputation analysis). Multivariable analyses highlighted sex, age, pain type, anxiety, depression, and quality of life levels as related factors associated with trajectories (**Table 3**).

4.2.1. Trajectory 1

Male patients and patients who do not suffer from fibromyalgia had a higher risk to belong to the “mild pain” trajectory compared with the “severe pain” trajectory (RR = 2.21, 95% CI [1.01–4.87], $P = 0.049$ and RR = 2.28, 95% CI [1.01–5.17], $P = 0.049$, respectively).

4.2.2. Trajectory 2

Patients with “moderate pain” were significantly older than patients with “mild pain” (53.7 ± 12.0 vs 46.1 ± 9.9 years, $P =$

Table 2**Initial baseline characteristics of patients (sample to last contact) stratified by trajectory with the last observation carried forward method.**

Characteristics	Trajectory 1 (16.0%)			Trajectory 2 (35.3%)			Trajectory 3 (48.7%)			P
	N	Number (%)	Mean (SD)	N	Number (%)	Mean (SD)	N	Number (%)	Mean (SD)	
Demographics										
Age (y)	42	—	46.1 (9.9)	87	—	53.7 (12.0)	127	—	50.0 (11.2)	0.008 ^{b1}
Sex (female)		23 (54.8)	—		71 (81.6)	—		100 (78.7)	—	0.002 ^{b1,b2}
Pain-related										
Pain type	42			87			127			
Fibromyalgia		12 (28.6)	—		37 (42.5)	—		66 (52.0)	—	0.03 ^{b2}
Peripheral neuropathic pain		15 (35.7)	—		21 (24.1)	—		36 (28.4)	—	0.39
Central neuropathic pain		2 (2.4)	—		9 (10.3)	—		9 (7.1)	—	0.27
Complex regional pain syndrome		8 (19.1)	—		11 (12.6)	—		10 (7.9)	—	0.13
Back pain, sciatica, cruralgia, neuralgia, pelvic pain, and gonarthrosis		5 (11.9)	—		7 (8.1)	—		4 (3.2)	—	0.09
Polyarthritis and spondylitis		0 (0)	—		0 (0)	—		1 (0.8)	—	0.60
Others		1 (2.4)	—		2 (2.3)	—		1 (0.8)	—	0.61
Pain status										
Score DN4* ≥ 4	37	26 (70.3)	—	72	57 (79.2)	—	117	103 (88.0)	—	0.03 ^{b2}
Average pain intensity	38	—	5.1 (1.9)	83	—	6.2 (1.6)	119	—	7.7 (1.3)	<0.001 ^{b1,b2,b3}
Average pain < 3	38	4 (10.5)	—	83	2 (2.4)	—	119	0 (0)	—	<0.001
Average pain [3-6]		26 (68.4)	—		45 (54.2)	—		20 (16.8)	—	
Average pain ≥ 7		8 (21.1)	—		36 (43.4)	—		99 (83.2)	—	
Number of painful peaks (median [IQR])	22	—	2.8 [2; 5]	43	—	3 [2; 5]	76	—	4 [3; 8.3]	0.011
Maximal pain intensity	39	—	7.1 (2.0)	84	—	7.8 (1.3)	121	—	8.8 (1.3)	<0.001 ^{b2,b3}
Maximal pain < 3		1 (2.6)	—		1 (1.2)	—		1 (0.8)	—	0.001
Maximal pain [3-6]		10 (25.6)	—		9 (10.7)	—		4 (3.3)	—	
Maximal pain ≥ 7		28 (71.8)	—		74 (88.1)	—		116 (95.9)	—	
Ketamine										
Patient profile (naive)	42	20 (47.6)	—	87	44 (50.6)	—	127	62 (48.8)	—	0.94
Administration (after baseline)										
Intravenous route	42	39 (92.9)	—	87	79 (90.8)	—	127	109 (85.8)	—	0.34
Cumulative dose (mg)† (median [IQR])	39	—	222 [105; 269.5]	79	—	245 [140; 269.5]	109	—	210 [100; 269.5]	0.03
Cumulative dose ≤ 222 (mg)		22 (56.4)	—		37 (46.8)	—		76 (69.7)	—	0.006 ^{b3}
Cumulative duration (d)† (median [IQR])	39	—	4 [3; 5]	79	—	3 [3; 5]	109	—	3 [3; 5]	0.75
≤ 3 d		19 (48.7)	—		43 (54.4)	—		57 (52.3)	—	0.84
≥ 4 d		20 (51.3)	—		36 (45.6)	—		52 (47.7)	—	
Emotional aspects										
HAD, anxiety symptoms score	39	—	7.7 (4.4)	82	—	10.3 (4.3)	120	—	11.0 (4.2)	<0.001 ^{b1,b2}
Score ≤ 7		20 (51.3)	—		26 (31.7)	—		27 (22.5)	—	0.11
Score [8-10]		7 (18.0)	—		22 (26.8)	—		28 (23.3)	—	
Score ≥ 11		12 (30.8)	—		34 (41.5)	—		65 (54.2)	—	
HAD, depression symptoms score	39	—	7.2 (4.7)	79	—	9.4 (4.4)	119	—	9.6 (4.4)	0.016 ^{b1,b2}
Score ≤ 7		22 (56.4)	—		31 (39.2)	—		42 (35.3)	—	0.17
Score [8-10]		7 (18.0)	—		20 (25.3)	—		26 (21.9)	—	
Score ≥ 11		10 (25.6)	—		28 (35.4)	—		51 (42.9)	—	
Quality of life										
SF-12—physical score	35	—	34.6 (8.5)	71	—	30.3 (6.8)	113	—	28.5 (8.2)	0.003 ^{b1,b2}
SF-12—mental score		—	41.4 (12.1)		—	38.1 (9.3)		—	37.9 (11.1)	0.35
Concomitant drugs										
Number of treatments	38	—	2.5 (2.0)	85	—	3.2 (1.7)	122	—	2.9 (1.7)	0.089
Treatment category	38			85			122			
Paracetamol/NSAIDs		14 (36.8)	—		35 (41.2)	—		55 (45.1)	—	0.64
Opioids step 2†, nefopam		11 (29.0)	—		45 (52.9)	—		53 (43.4)	—	0.04 ^{b1}
Opioids step 3§		5 (21.1)	—		12 (14.1)	—		15 (12.3)	—	0.40
Antidepressants		22 (57.9)	—		58 (68.2)	—		66 (54.1)	—	0.12
Antiepileptics		10 (26.3)	—		24 (28.2)	—		34 (27.9)	—	0.98
Adjuvants		6 (15.8)	—		18 (21.2)	—		27 (22.1)	—	0.70
Hypnotics/sedatives		6 (15.8)	—		13 (15.3)	—		18 (14.8)	—	0.99

(continued on next page)

Table 2 (continued)

Characteristics	Trajectory 1 (16.0%)			Trajectory 2 (35.3%)			Trajectory 3 (48.7%)			P
	N	Number (%)	Mean (SD)	N	Number (%)	Mean (SD)	N	Number (%)	Mean (SD)	Global
Anxiolytics	7	18.4	—	26	30.6	—	26	21.3	—	0.21
Antipsychotics	2	5.3	—	6	7.1	—	5	4.1	—	0.65
None	7	18.4	—	3	3.5	—	9	7.4	—	0.02

Data are expressed as mean $\pm$ SD, as median [interquartile range] and as effective (percentage). The continuous variables were compared between trajectories groups by ANOVA or the Kruskal–Wallis test. When appropriate, Tukey–Kramer and Dunn post hoc tests were performed taking into account multiple comparisons. The comparisons were performed using χ^2 or Fisher exact tests for categorical variables. When appropriate, a post hoc test was performed (Marascuilo procedure).

* DN4: except for fibromyalgia.

† Patient with intravenous route only.

‡ Opioids step 2: dihydrocodeine; ibuprofen-codeine; paracetamol-codeine; paracetamol-opium; paracetamol-opium-caffeine; paracetamol-tramadol; tramadol; and tramadol-dextropropofol.

§ Opioids step 3: morphine; oxycodone; fentanyl; and buprenorphine.

Intergroup analysis with b1 corresponds to trajectory 1 vs trajectory 2, b2 corresponds to trajectory 1 vs trajectory 3, and b3 corresponds to trajectory 2 vs trajectory 3 ($P < 0.05$).

0.002). The proportion of female patients was higher than patients with “mild pain” (81.6%, 71/87 vs 54.8%, 23/42, $P < 0.05$). These results were confirmed by multivariable analysis (age: RR = 1.05, 95% CI [1.01–1.09], $P = 0.006$; sex: RR = 2.85, 95% CI [1.19–6.81], $P = 0.019$). These patients had a higher level of anxiety (10.3 ± 4.3 vs 7.7 ± 4.4 , $P = 0.008$) and depression (9.4 ± 4.4 vs 7.2 ± 4.7 , $P = 0.041$) than patients with “mild pain,” with a poorer physical quality of life (SF-12 mean score: 30.3 ± 6.8 vs 34.6 ± 8.5 , $P = 0.032$).

4.2.3. Trajectory 3

Patients with “severe pain” were mostly women (78.7%, 100/127), and women had a higher risk to belong to this trajectory than to “mild pain” trajectory (RR = 2.21, 95% CI [1.01–4.87], $P = 0.049$). Half of patients belonging to trajectory 3 were suffering from fibromyalgia (52.0%, 66/127). Patients with fibromyalgia had a higher risk to belong to this trajectory than to “mild pain” trajectory (RR = 2.28, 95% CI [1.01–5.17], $P = 0.049$). Intensity of pain paroxysms was higher than when compared with “mild” and “moderate pain” trajectories ($P < 0.001$), with a higher anxiety and depression level ($P < 0.001$ and $P = 0.019$, respectively), and a poorer physical quality of life than patients with “mild pain” ($P = 0.001$) confirmed by the multivariable analysis (RR = 0.92, 95% CI [0.86–0.97], $P = 0.003$). Finally, a greater proportion of patients with “severe pain” (69.7%, 76/109) received a cumulative dose of ketamine ≤ 222 mg (Table 2). Concerning patients with intravenous route, the multivariate analysis confirmed that patients who received a cumulative dose > 222 mg had a higher risk to be in the “mild pain” trajectory than the “severe pain” trajectory (RR = 2.51, 95% CI [1.31–4.83], $P = 0.006$).

5. Discussion

This study in 256 patients suffering from refractory chronic pain explored in real-life pain relief with 1 ketamine delivery procedure. It showed (1) an overall initial diminution of pain that was maintained for 1 year, (2) 3 distinct pain trajectories characterized by demographic and clinical variables, (3) various ketamine delivery procedures, (4) a good tolerance to ketamine, and (5) the concomitant use of a number of drug and nondrug treatments.

It is the first time a study follows patients with chronic pain and ketamine treatment beyond 3 months.^{33,34} For the overall population, a significant initial pain relief was observed with just 1 ketamine delivery procedure and was maintained for 1 year. The study allowed also to identify 3 distinct pain trajectories that bring more precise information on patients’ pain pathways. A small proportion of patients (16%, trajectory 1) were indeed improved with ketamine. Other patients (trajectories 2 and 3), despite a significant initial pain decrease for a few months, were still with moderate to

severe pain throughout the year. The identification of these trajectories has allowed to highlight different profiles of patients. We observed that patients with neuropathic pain characteristics were more likely to be in the “mild pain” trajectory and therefore could respond more favorably to ketamine. Conversely, patients with fibromyalgia were more at risk to be in the “severe pain” trajectory with a higher level of anxiety and depression and a poorer quality of life. It is also interesting to note that patients with neuropathic pain and fibromyalgia were present in all trajectories, suggesting that different subtypes may exist within the same type of pain and may respond differently to ketamine. These findings may shed a light on the controversial results of ketamine analgesic effect described in the literature.^{10,23,30} Likewise, a recent double-blind randomized clinical trial of our group in 20 patients with chronic refractory neuropathic pain showed different patient responses to ketamine that could be linked to the patients’ phenotype, genotype, and/or ketamine pharmacology.³² The existence of fibromyalgia clusters^{1,29,31,41} and of phenotypic subgroups of patients with neuropathic pain has also been suggested.^{3,5,14} These collective information suggest a multilayer complexity of ketamine in chronic pain treatment linked to the patient, the type of pain, and the drug metabolism.

A majority of patients reported moderate to severe anxiety (168/241, 69.7%) and depression (142/237, 59.9%) with an impaired quality of life compared with the general population (mean physical health score: 32.2 ± 7.8 vs 51.2 ± 7.4 ¹⁷ and mean mental health score: 38.5 ± 10.7 vs 48.4 ± 9.4 ¹⁹). A gradient in the level of anxiety, depression, and quality of life was observed according to pain trajectories. The most painful patients (trajectories 2 and 3) were the most anxious, most depressed, with a poorer quality of life, items that do influence ketamine response.³⁶

We collected various ketamine delivery procedures across and within pain clinics. Optimizing ketamine administration remains a challenge considering the diversity of infusion protocols because of the lack of direct comparisons.²³ The literature suggests that a single dose of 0.5 mg/kg may be too low to provide a long-term analgesic or antidepressant effect.^{10,32} In this study, we showed that higher doses may provide a better benefit because patients in the “mild pain” trajectory had pain relief and a cumulative dose of ketamine > 222 mg (median dose).

Ketamine was well tolerated with transient adverse events that have previously been reported.² However, there is a lack of data regarding repeated administration of ketamine at higher doses in chronic pain. Further studies should now focus on the dose-response of ketamine with repeated administrations, which may have a greater effect than a single infusion, a phenomenon seen with moderate evidence in depression.¹³

Patients had polypharmacy that may lead to possible drug interactions and influence ketamine response because ketamine metabolism involves cytochromes P450.⁸ Moreover, it is

Table 3**Multivariable analyses to characterize each pain trajectory.**

Trajectory	Variables	Relative risk (RR)	95% confidence interval	P
Model 1				
1 vs 2	Age	1.05	1.01-1.09	0.006
	Female (vs. male)	2.85	1.19-6.81	0.019
	Fibromyalgia	1.63	0.68-3.91	0.274
1 vs 3	Age	1.03	0.99-1.06	0.136
	Female (vs. male)	2.21	1.01-4.87	0.049
	Fibromyalgia	2.28	1.01-5.17	0.049
2 vs 3	Age	0.98	0.95-1.01	0.056
	Female (vs. male)	0.78	0.38-1.60	0.492
	Fibromyalgia	1.40	0.77-2.53	0.266
Model 2				
1 vs 2	Age	1.05	1.01-1.10	0.019
	Female (vs. male)	3.24	1.17-8.95	0.023
	Fibromyalgia	1.23	0.44-3.43	0.691
	Hospital Anxiety and Depression Scale—anxiety score	1.07	0.92-1.23	0.385
	Hospital Anxiety and Depression Scale—depression score	1.04	0.90-1.19	0.611
1 vs 3	12-Item Short-Form health survey physical score	0.95	0.89-1.00	0.068
	Age	1.04	0.99-1.08	0.075
	Female (vs. male)	2.82	1.08-7.34	0.034
	Fibromyalgia	1.40	0.52-3.75	0.502
	Hospital Anxiety and Depression Scale—anxiety score	1.11	0.97-1.28	0.121
2 vs 3	Hospital Anxiety and Depression Scale—depression score	1.01	0.88-1.15	0.902
	12-Item Short-Form health survey physical score	0.92	0.86-0.97	0.003
	Age	0.99	0.96-1.02	0.363
	Female (vs. male)	0.87	0.39-1.94	0.731
	Fibromyalgia	1.14	0.59-2.20	0.700
	Hospital Anxiety and Depression Scale—anxiety score	1.05	0.95-1.15	0.339
	Hospital Anxiety and Depression Scale—depression score	0.97	0.89-1.06	0.523
	12-Item Short-Form health survey physical score	0.97	0.96-1.01	0.116

Data are expressed as relative risk [95% CI]. To determine the parameters associated to pain trajectories in multivariable analyses, multinomial polytomous logistic regression was performed.

questionable whether the benefit/risk balance of these treatments is optimal because of the presence of persistent pain, anxiety, and depression. During the study, more than 60% of patients found that nonpharmacological approaches improved their condition. Several studies have highlighted the importance of nonpharmacological practices, such as physical exercise (as a first-line treatment) in fibromyalgia.³⁸

Our data collection in a large sample of patients with chronic pain, over a long period in real-life conditions, allowed us for the first time to make an inventory of ketamine delivery procedures in French pain structures. The observational design of the study has known biases, although observational research is valuable in bringing information needed to improve medical decision-making.⁶ The open-label design, the lack of a control or placebo, and missing data linked to unanswered phone calls represent limitations. The National Research Council recommends imputation of missing data combined with a sensitivity analysis to demonstrate the robustness of the imputation. To guarantee the robustness of results and to confirm that conclusions could be supported by data despite missing (at random) data, 3 sensitivity analyses were conducted. These showed similar pain trajectories, and analyses on ketamine responders showed statistical difference in 30 and 50% pain intensity reduction between trajectories. Furthermore, it is interesting to observe that although

36% of participants completed the 12-month study, 70% of the whole sample had more than half of pain evaluation data.

In conclusion, this real-life study in patients with chronic pain identified distinct pain relief trajectories with variables that may be predictive of the response to ketamine according to pain characteristics, level of anxiety, depression, or quality of life. It also showed that higher ketamine doses are more efficient than lower doses and that tolerance is good across the various protocols used in the pain clinics. To optimize the management of refractory chronic pain with ketamine, it seems now pivotal to study further and optimize the subtyping of patients before ketamine administration to provide the most effective and safe treatment in this vulnerable population.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

The authors thank all participating patients for their continued commitment to the study and all the residents/interns of the Clinical Investigation Platform/Clinical Investigation Center Inserm 1405 for their contribution.

OKAPI Consortium: Thibault Riant^d, Bruno Rioult^d, Marc Sorel^e, Christian Gov^f, Pascale Vergne-Salle^g, Franck Le Caër^h, Maryline Feuilletⁱ, Fadel Maamar^j, Gilles Allano^k, Julien Esnault^l, Véronique Dixneuf^l, Jacques Gaillard^m, Olivier Collardⁿ, Mario Barmaki^o, Gilbert André^p, Claire Delorme^q, Frédéric Plantevin^r, Caroline Maindet^s, Yves-Marie Pluchon^t, Xavier Kieffer^u, Jean-Marie Amodeo^v, Yannick Perier^w, Mohamed El Ayadi^x, Florence Tiberghien^y, Sonia Cieslak^z, Erik Vassort^{aa}, Géraldine Demontgazon^{ab}, Jean-Marie Le Borgne^{ac}, Caroline Colomb^{ad}, Rodrigue Deleens^{ae}, Virginie Piano^{af}, and Julien Nizard^{ag}.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PAIN/B429>.

Article history:

Received 3 August 2020

Received in revised form 24 June 2021

Accepted 30 June 2021

Available online 20 July 2021

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