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ORIGINAL ARTICLE

Ketamine in chronic pain: A Delphi survey

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Abstract

Background: There is no recommendation in Europe for the use of ketamine in patients with chronic pain. The heterogeneity of practice highlights the need to seek the advice of experts in order to establish a national consensus. This Delphi survey aimed to reach a national consensus on the use of ketamine in chronic pain in Pain clinics.

Methods: A collaborative four-round internet-based questionnaire was used. It was created after literature search on ketamine administration in chronic pain and included about 96 items. It discussed utility and advantages, adverse events and deleterious aspects, methods of administration, concomitant treatments and assessment of results.

Results: Twenty-eight experts completed all rounds of the survey with a total of 81.3% items reaching a consensual answer. Neuropathic pain represents the first indication to use ketamine, followed, with a good to moderate utility, by other situations (fibromyalgia, complex regional pain syndrome, central neuropathic pain, peripheral neuropathic pain, nociceptive pain, sensitization, opioid withdrawal, palliative care, depression). Experts agreed on the rare occurrence of adverse events. Concerning routes of administration, intravenous infusion with doses of 0.5–0.9 mg/kg/d for 4 days of treatment is preferred. Place of care is hospital, as in- or out-patient, with a quarterly administration of ketamine. Finally, ketamine effectiveness is assessed 1 month after infusion, and experts encourage combination with non-pharmacological treatment.

Conclusions: This Delphi survey established a consensus of pain specialists on the use of ketamine in refractory chronic pain, thus providing a basis for future comparative trials.

Significance: This Delphi survey in chronic pain reached agreement on four main aspects: (1) Priority to treat neuropathic pain with evaluation of effectiveness at 1 month; (2) No deleterious effects in the majority of listed diseases/situations with the absence or <3% of suggested adverse events; (3) 0.5–0.9 mg/kg/d IV infusion; (4) Combination with non-pharmacological treatment.

1 | INTRODUCTION

Chronic pain remains difficult to treat and the efficacy of recommended treatments is limited (Finnerup et al., 2015). Clinicians in Pain clinics often resort to other drugs for chronic pain, like ketamine, a general anesthetic agent and *N*-methyl-D-aspartate (NMDA) receptor antagonist. Ketamine has been used as an analgesic drug for the last decades in neuropathic pain (Eichenberger et al., 2008; Gottrup et al., 2006; Jørum et al., 2003; Lemming et al.,

2005, 2007; Mercadante et al., 2000; Nikolajsen et al., 1996; Rabben et al., 1999), nociplastic pain, fibromyalgia (Graven-Nielsen et al., 2000; Sörensen et al., 1996), complex regional pain syndrome (CRPS) (Schwartzman et al., 2011; Sigtermans et al., 2009) or migraine (Nicolodi & Sicuteri, 1995).

Over the past two decades, several reviews and studies have been published on ketamine for chronic pain with different dosages, routes of administration, infusion durations and various aetiologies (Michelet et al., 2018; Cohen

et al., 2018; Pickering et al., 2018). Indeed, guidelines present evidence to support the use of ketamine in chronic pain, but these recommendations were often based on small randomized trials, retrospective and observational studies (Cohen et al., 2018; Tran and McCormack, 2020). A recent survey describes a reference protocol in CRPS that could require further studies to validate their nine recommendations (Xu et al., 2019). Recent systematic reviews or meta-analyses in patients with chronic pain (phantom limb pain, post-spinal cord injury, CRPS I and II, cancer pain, fibromyalgia) including 3 to 21 randomized clinical trials (RCTs) (211 to 548 patients) present small positive effect of ketamine that may vary widely among chronic pain patients (Aiyer et al., 2018; Bell & Kalso, 2018; Michelet et al., 2018; Orhurhu et al., 2019; Zhao et al., 2018). There is a great heterogeneity among studies, the absence of blinding due to ketamine side effects not allowing a high level of evidence. The recent literature remains controversial with positive (Lumanauw et al., 2019) or limited results of ketamine in neuropathic pain (Pickering et al., 2020). An observational study however reports the pain trajectories of 256 patients with chronic pain, their pain relief with ketamine over 1 year and the heterogeneity of care (Corrigger et al., 2021). Without any consensus in Europe and with limited recommendations for the use of ketamine in patients with chronic pain, it is necessary for good clinical practice to properly define ketamine administration criteria that can be consistently and systematically implemented for different chronic pain conditions. For this purpose and in the absence of a 'gold standard' for ketamine treatment, the most reliable method is a stepwise process consisting of a Delphi survey, to form an expert consensus. This method seems to be an appropriate preliminary approach which would be then validated by further external studies. The advantage of the Delphi study is that it would indicate the use of ketamine in real life and with the experts reporting their experience could promote and guide best practice.

Therefore, this study, focussing on a Delphi survey and expert consensus, was conducted to reach a French national consensus on the use of ketamine administration in chronic pain, considering both the beneficial and the deleterious aspects of this molecule in clinical pain clinics.

2 | METHODS

2.1 | Study design

Following international guidelines (Hasson et al., 2000), this Delphi survey aims to reach a convergence or consensual response of opinion among experts on a pre-established theme over a series of rounds (Green et al.,

1999; Powell, 2003). It is a group facilitation technique that is commonly used in health and social sciences. In recent years, online methods have been used more frequently and have provided several advantages including anonymity of the experts, faster set-ups and recruitment phases or better data reliability (survey responses being entered directly into associated databases) (Gill et al., 2013).

2.2 | Delphi experts

The original expert panel consisted of 34 pain physicians working in chronic pain clinics (where are referred severe chronic pain patients), selected because of their specific expertise in using ketamine for chronic pain. The participants were selected on their experience and familiarity with the administration of ketamine (clinical experience for more than 5 years; different medical specialties), their scientific activity in this domain of pain treatment and their active participation in the French Pain Society (SFETD). Several physicians had already taken part in studies with ketamine. Moreover, the majority of experts participated as co-investigators of a national observational study in patients with chronic pain (OKAPINCT033119238, Corrigger et al., 2021). With a total of 585 patients treated with ketamine, their participation provided additional information to confirm their eligibility to participate. To minimize any selection bias among the experts and to increase the external validity of the survey, they came from different medical initial specialty.

An invitation to take part to a four-round Delphi survey was sent by email, explaining the purpose of the study, the expected time commitment and the timelines of the web-based survey (using the RedCap software application at <https://redcap.chu-clermontferrand.fr>). Participants remained anonymous during all rounds of the Delphi survey, and they were not contacted during the study other than to share the study phases. No time limit was imposed on the participants for replying to the questionnaire.

2.3 | Survey

The survey was constructed by two pain clinicians, each with more than 15 years of clinical and research experience in pain management and use of ketamine. It included four rounds. The survey was guided by a systematic evaluation of the current literature on chronic pain management by ketamine. The PubMed, Medline, Google Scholar and Cochrane databases were searched until August 2021 for peer-reviewed articles, using the following keywords: "ketamine AND chronic pain", "ketamine AND fibromyalgia", "ketamine AND CRPS", "ketamine

AND nociceptive pain”, “ketamine AND sensitization”, “ketamine AND chronic pain”, “ketamine AND opioid withdrawal”, “ketamine AND palliative care”, “ketamine AND depression”, “ketamine AND adverse event”, “ketamine AND infusion”, “ketamine AND per os”, “ketamine AND intranasal”, “ketamine AND subcutaneous”. Several pieces of information were collected including the aetiology of chronic pain, ketamine protocol (route, dosage, duration of administration), main endpoint, results and adverse events. The original questionnaire was constructed following all of these criteria but also through the knowledge of the protocols used in the OKAPI study cited above.

Initially, demographic information of participants was recorded, including gender, age, medical specialty, years of clinical experience and years of specific experience with the use of ketamine for chronic pain. The survey discussed the following topics about ketamine: (1) Utility and advantages; (2) Adverse events and deleterious aspects; (3) Methods of administration; (4) Concomitant treatment and (5) Assessment of results. These themes were divided into 15 questions, each of them proposing 3 to 12 items for a total of 96 items to be scored according to the proposed scales (Table 1). In parallel, descriptive data were collected (non-Delphi section) on aspects of current practice to complete the profile of experts (frequency, prescription and care habits); results were analysed separately from the rest of the Delphi survey.

In the first Delphi round, the experts who gave their agreement to participate received an e-mail with a link to the online survey. In this round, panelists were asked to answer every question of the initial questionnaire. The expert selected from a pre-established list the answer that seemed most representative of his/her experience. Several type of scales were used: 5, 7 or 9 point Likert-type ordinal scales with nuances in the used adjectives, percentage scales divided in different sections depending on the items and a differential semantic scale for the purpose of prioritization to treat (Table 1).

For the second round, all Round 1 data were collected, reviewed and refined by the investigator team into a new, more concise questionnaire. This was distributed as Round 2 of the Delphi process to ‘round 1 participants’ who agreed to participate further. An e-mail was sent that included a detailed invitation to participate and web link to the online survey. All topics (utility and advantages, adverse events and deleterious aspects, methods of administration, concomitant treatment, and assessment of results) were again covered with a restriction in choice (answers <1st quartile removed). Responses used by $\geq 70\%$ of participants were considered as consensual and omitted from the list for further evaluation.

The third round was conducted like the second round for responses <1st quartile and consensual data. In this round, participants had to self-evaluate their skills (i.e. ‘weak’, ‘moderate’, ‘strong’, ‘excellent’) on each question with an opportunity to comment.

A fourth and final consensual round was built following the results of the previous round. A new restriction in choice was applied about weak and moderate skills in order to target the most relevant answers. Responses agreeing with less than 70% were analysed: the investigator team proposed an answer and asked experts if they agreed or disagreed with it. For each item, the experts had the possibility to comment their answers.

2.4 | Statistical analysis

Data from round two, three and four were exported to an excel spread sheet and analysed on SAS 9.4 (SAS Institute, Cary, NC, USA). Overall support for group responses to questions was reported as mean and standard deviation. Consensus in Delphi surveys is considered to have been achieved when a given proportion of participants agree on an item under debate; this proportion varies between studies (Boonen et al., 2009; Ferguson et al., 2008; Hasson et al., 2000; Smith et al., 2012). In the absence of standardized guidelines, consensus levels must be set arbitrarily according to the importance of the study outcomes (Powell, 2003). For this study, consensus level with $\geq 70\%$ agreement was considered as a ‘good’ consensus status, and ‘strong’ consensus was assumed when $\geq 90\%$ or more of participants agreed.

3 | RESULTS

The full four-round Delphi process and analysis included 34 experts who agreed to participate in the Delphi process and provided questions and valid email address for subsequent rounds. Respectively, 32/34 (response rate, 94%), 31/32 (97%), 29/31 (94%) and 28/29 (97%) respondents replied to Rounds 1, 2, 3 and 4 (Figure 1). Demographics of participants are described in Table 2.

3.1 | Utility, advantages and effectiveness

3.1.1 | Delphi

Among the list of proposed diseases/situations potentially treated with ketamine, 74.2% of experts have

TABLE 1 Initial questionnaire

Questions	Items	Scales
1. In your opinion, is ketamine useful in the following situations or diseases?	1,FM 2,CRPS 3,CNP 4,PNP 5, Nociceptive pain 6, Sensitization situations 7, Opioid withdrawal 8, Palliative care 9, Depression	1, Excellent 2, Very good 3, Good 4, Average 5, Weak 6, Very weak 7, None
2. In your opinion, is ketamine deleterious in the following situations or diseases?	1,FM 2,CRPS 3,CNP 4,PNP 5, Nociceptive pain 6, Sensitization situations 7, Opioid withdrawal 8, Palliative care 9, Depression	1, Extremely 2, Very Strongly 3, Strongly 4, Moderately 5, Weak 6, Very weak 7, Not at all
3. In your opinion, what percentage of patients find a benefit with ketamine in the following situations or diseases?	1,FM 2,CRPS 3,CNP 4,PNP 5, Nociceptive pain 6, Sensitization situations 7, Opioid withdrawal 8, Palliative care 9, Depression	1,0–25% 2,26–50% 3,51–75% 4,76–100%
4. Do you think ketamine has any adverse effects in the following situations or diseases?	1,FM 2,CRPS 3,CNP 4,PNP 5, Nociceptive pain 6, Sensitization situations 7, Opioid withdrawal 8, Palliative care 9, Depression	1, Always 2, Most times 3, Very often 4, Often 5, Sometimes 6, Rarely 7, Never
5. What percentage of patients do you think have the following adverse events?	1, Headache 2, Bad trip 3, Psychotic effects 4, Exacerbation of pain 5, Addiction 6, Interstitial cystitis 7, Liver injury 8, Constipation 9, Vein inflammation 10, Hypertension	1,0% 2,<3% 3,>3–25% 4,26–50% 5,51–75% 6,76–100%
6. In your opinion, which is the preferred mode of administration?	1,IV bolus 2,IV infusion 3,IV bolus+IV infusion 4, SC 5, SC+IV bolus 6,SC+IV infusion 7,SC+IV bolus +IV infusion 8,PO 9,PO bolus+SC 10, Intranasal	1, Always 2, Most times 3, Very often 4, Often 5, Sometimes 6, Rarely 7, Never
7. What dose and mode of administration do you think it takes to make ketamine effective?	1,IV bolus 2,IV infusion 3,IV bolus+IV infusion 4, SC 5, SC+IV bolus 6,SC+IV infusion 7,SC+IV bolus +IV infusion 8,PO 9,PO bolus+SC 10, Intranasal	1, <0.5 mg/kg/j 2,0.5–0.9 mg/kg/j 3,1–1.4 mg/kg/j 4,>1.5 mg/kg/j
8. In your opinion, what is the optimal duration of administration of ketamine?	1, Duration of administration	1, One day 2, Two days 3, Three days 4, Four days 5, More than four days
9. In your opinion, how relevant is the place where ketamine can be administered?	1, At home 2, Hospital in-patient 3, Hospital out-patient	1, Excellent 2, Very good 3, Good 4, Average 5, Weak 6, Very weak 7, None
10. What do you think is the most relevant length of stay?	1, Length of stay	1, One day 2, Two days 3, Three days 4, Four days 5, More than four days
11. What do you think is the most relevant repetition of ketamine intake?	1, Repeat of ketamine intake	1, Everyday 2, Weekly 3, Monthly 5, Quarterly 6, Half-year 7, Annual
12. In your opinion, what is the relevance of associating the following treatments with ketamine?	1, Paracetamol 2,NSAIDs 3, Nefopam 4, Weak opioid 5, Morphine 6, Other strong opioid 7, Oxygen 8, Nitrous oxide 9, Setron 10, Amantadine 11, Lidocaine (iv) 12, Magnesium	1, Excellent 2, Very good 3, Good 4, Average 5, Weak 6, Very weak 7, None
13. In your opinion, what is the relevance of combining non-pharmacological treatment with ketamine?	1, Combining non-pharmacological treatment	1, Excellent 2, Very good 3, Good 4, Average 5, Weak 6, Very weak 7, None

(Continues)

classified ‘neuropathic pain’ as the first indication to use ketamine. At the end of the four rounds, experts agreed about the utility of ketamine in all different situations/

diseases. In fact, a ‘good utility’ was described in central neuropathic pain (CNP), peripheral neuropathic pain (PNP), opioid withdrawal, palliative care and depression

TABLE 1 (Continued)

Questions	Items	Scales
14. In your opinion, how long after administration should the effectiveness of ketamine be evaluated?	1, Evaluation of effectiveness	1, Immediately to 24 h 2, 2-4 days 3, 5-7 days 4, 10 days 5, 15 days 6, 1 month 7, 2 months 8, 3 months 9, Not required
15. In your opinion, what are the situations and diseases that should be treated with ketamine in order of priority (1, highest priority to 10, least priority)?	1, NP 2, FM 3, CRPS 4, Headache 5, Back pain 6, Cancer 7, Pelvic pain 8, Sensitization situations 9, Opioid withdrawal	1, 2, 3, 4, 5, 6, 7, 8, 9

Abbreviations: FM, Fibromyalgia; Complex Regional Pain Syndrom (CRPS); CNP, Central Neuropathic Pain; PNP, Peripheral Neuropathic Pain; IV, Intravenous; SC, Subcutaneous; PO, Per Os.

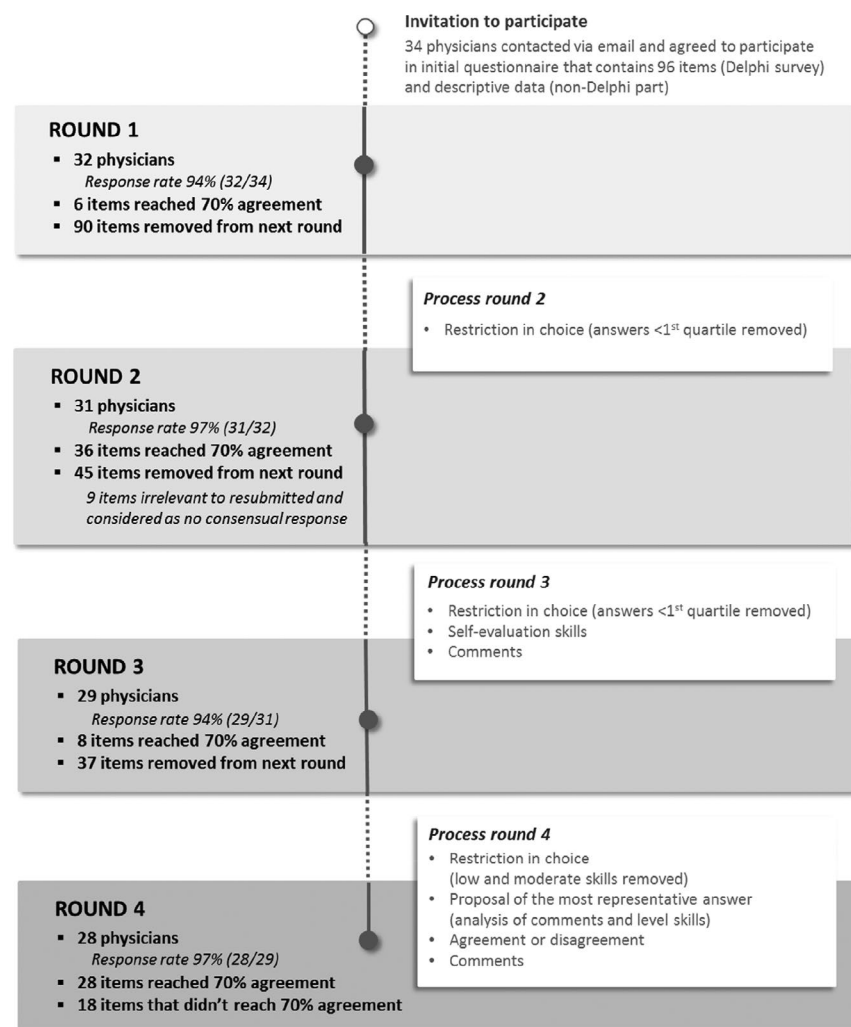


FIGURE 1 Flowchart of Delphi process

while 'a moderate utility' was found in fibromyalgia (FM), CRPS, nociceptive pain and sensitization situations. The percentage of patients with positive report ranged from 26% to 75% according to suggested diseases/situations with a maximum percentage in CNP, PNP and palliative care. Finally, 77.4% of experts agreed about evaluation of effectiveness which must be done at 1 month (see Table 3 for more details).

3.1.2 | Descriptive data

Regardless of the Delphi survey, descriptive data were collected to bring further information. In this context, ketamine would decrease the pain score by an average of 3.4 ± 1.3 with a relatively close distribution between the situations/diseases (min: 3.0 ± 1.3 in nociceptive pain; max: 3.7 ± 1.3 in palliative care). The vast majority

TABLE 2 Demographics of participants (round 1)

	<i>n</i> (%)
Gender	
Male	20 (62.5)
Female	12 (37.5)
Age (mean \pm SD)	53.9 (7.3)
Initial specialty	
General Practitioner	11 (34.4)
Anesthesiology	8 (25.0)
Rheumatology	5 (15.6)
Other	5 (15.6)
Neurology	2 (6.3)
Palliative care	1 (3.1)
Experience in Pain treatment (years)	
5–9	5 (15.6)
10–14	5 (15.6)
15–19	12 (37.5)
20+	10 (31.3)
Activity in algology	
Full time	26 (81.3)
Part time	6 (18.8)
Place of activities	
Out-patient pain clinic	21 (65.6)
In-patient pain clinic	11 (34.4)
Total of patients followed in the centre (mean \pm SD)	2016 \pm 1525
Median	1500
Percent of patients treated by ketamine in the pain clinic	
1–25%	23 (83.1)
26–50%	4 (12.5)
76–100%	1 (3.1)
Unknown	1 (3.1)
Total of patients followed (mean \pm SD)	614 \pm 441
Median	500
Percent of patients treated by ketamine by the expert	
1–25%	27 (84.4)
26–50%	4 (12.5)
76–100%	1 (3.1)
Total of patients treated by ketamine by expert (mean \pm SD)	142 \pm 138
Median (Min, Max)	68 (18,1320)

Abbreviation: SD, standard deviation.

of experts reported that ketamine would be effective in preventing pain before surgery (86.7%) and that its effectiveness was sometimes due to the placebo effect

(62.5%). As part of the evaluation of results, a list of commonly evaluated items was proposed to the experts: pain intensity, pain evolution, mood and sleep were chosen by more than 80% of experts. Hepatic assessment, handicap and fatigue were selected by 60 to 70% of experts. Finally, some experts described an increase in mobility as ‘Weak’ or ‘Moderate’ regardless of the situations/diseases suggested apart from patients in opioid withdrawal for whom increased mobility appears to be more important (see Table S1, which describes descriptive data).

3.2 | Adverse events and deleterious aspects

3.2.1 | Delphi

Ketamine was not considered to be deleterious in six diseases/situations (‘Not at all’ in CRPS, CNP, PNP, nociceptive pain, opioid withdrawal and palliative care) and would be ‘weakly deleterious’ in depression. Regarding the frequency of adverse events, seven diseases/situations presented the answer ‘rarely to sometimes’ (in CRPS, CNP, PNP, nociceptive pain, opioid withdrawal, palliative care, and depression) whereas the answer ‘Sometimes’ was described in FM and sensitizations situations. Moreover, in the proposed list of adverse events, five items would never appear to occur or would occur in less than 3% of cases (‘0% to <3%’ of exacerbations of pain, interstitial cystitis, liver injury, constipation, vein inflammation). With consensual agreement of the experts, headache, bad trip, psychotic effects and addiction occurred in less than 3% of patients (Table 3).

3.3 | Methods of administration

3.3.1 | Delphi

Another topic where experts reached unanimous agreement was the route of administration with ‘IV infusion’ used ‘Most times to always’ with dosage of ‘0.5–0.9 mg/kg/d’. Consensual answers were also found about ‘SC’ used ‘Sometimes’ while ‘PO’ and the association of ‘IV bolus+IV infusion’ were used ‘Rarely’. The recommended dosage for both routes of administration, with respectively 85.0% and 77.8% of experts’ response, was ‘0.5–0.9 mg/kg/d’. Other proposed routes or association of routes were never chosen with a $\geq 70\%$ agreement. Regarding duration, experts agreed with 73.7% of answers that optimal duration of administration of ketamine was ‘4 days’.

TABLE 3 Consensual results of the four rounds

	Questions	Items	Answers	Consensus (%)	
INDICATION	Priority to treat	Q15	Neuropathic pain	Highest priority (1)	74.2
UTILITY	According to indication	Q1	FM	Moderate	70.4
			CRPS	Moderate	84.6
			CNP	Good	74.2
			PNP	Good to very good	100
			Nociceptive pain	Moderate	77.4
			Sensitization situations	Moderate	81.5
			Opioid withdrawal	Good	100
			Palliative care	Good	95.2
			Depression	Good	77.8
ADVANTAGES	% patients with positive report	Q3	CRPS	30%	80.0
			CNP	50%	84.6
			PNP	26–50%	71.4
			Sensitization situations	30%	84.2
			Opioid withdrawal	40%	90.0
			Palliative care	51–75%	80.8
			Depression	40%	76.5
EFFECTIVENESS		Q14	Evaluation of effectiveness	1 month	77.4
DELETERIOUS ASPECTS	According to indication	Q2	CRPS	Not at all	80.7
			CNP	Not at all	77.4
			PNP	Not at all	77.4
			Nociceptive pain	Not at all	82.6
			Opioid withdrawal	Not at all	77.4
			Palliative care	Not at all	83.3
			Depression	Weak	73.1
ADVERSE EVENTS	Frequency according to indication	Q4	FM	Sometimes	71.0
			CRPS	Rarely to sometimes	100
			CNP	Rarely to sometimes	100
			PNP	Rarely to sometimes	100
			Nociceptive pain	Rarely to sometimes	100
			Sensitization situations	Sometimes	71.0
			Opioid withdrawal	Rarely to sometimes	100
			Palliative care	Rarely to sometimes	100
			Depression	Rarely to sometimes	100
% patients with these adverse events		Q5	Headache	< 3%	82.1
			Bad trip	< 3%	80.8
			Psychotic effects	< 3%	84.6
			Exacerbation of pain	0% to <3%	100
			Addiction	< 3%	71.0
			Interstitial cystitis	0% to <3%	100
			Liver injury	0% to <3%	100
			Constipation	0% to <3%	100
			Vein inflammation	0% to <3%	100

TABLE 3 (Continued)

	Questions	Items	Answers	Consensus (%)
METHODS OF ADMINISTRATION <i>Route</i>	Q6	IV infusion	Most times to always	100
		SC	Sometimes	72.0
		IV bolus +IV infusion	Rarely	80.7
		PO	Rarely	82.6
		SC +IV bolus	Never	80.8
		SC +IV infusion	Never	84.6
		SC +IV bolus +IV infusion	Never	88.0
		SC +PO	Never	73.1
		Intranasal	Never	76.9
<i>Dose</i>	Q7	IV infusion	0.5 – 0.9 mg/kg/d	71.0
		SC	0.5 – 0.9 mg/kg/d	85.0
		IV bolus+IV infusion	0.5 – 0.9 mg/kg/d	77.8
<i>Duration</i>	Q8	Duration of administration	4 days	73.7
<i>Settings for pain care</i>	Q9	Hospital in-patient	Excellent	82.8
		Hospital out-patient	Very good to excellent	100
		At home	None	80.0
<i>Repetition</i>	Q11	Repeat of ketamine intake	Quarterly	70.8
Concomitant Treatments	Q12	Morphine	Good	85.2
		Other strong opioid	Good	84.6
		Magnesium	Good	93.3
		Weak opioid	Average	78.6
		Paracetamol	Weak	85.7
		NSAIDs	Weak	78.6
		Nefopam	Weak	92.3
		Oxygen	None	80.0
		Nitrous oxide	None	83.3
		Setron	None	79.3
Amantadine	None	83.3		
	Q13	Combining non-pharmacological treatment	Excellent	78.6

Abbreviations: FM, Fibromyalgia; Complex Regional Pain Syndrom (CRPS); CNP, Central Neuropathic Pain; PNP, Peripheral Neuropathic Pain; IV, Intravenous; SC, Subcutaneous; PO, Per Os.

In-patient care settings was the most recommended place to use ketamine with ‘Excellent’ for 82.8% of experts. The out-patient care setting was considered to be ‘Very good’ to ‘Excellent’ while treatment with ketamine at home was not recommended. Finally, 70.8% of experts agreed about a ‘Quarterly’ administration of ketamine intake (Table 3).

3.4 | Concomitant treatments

3.4.1 | Delphi

The association of strong opioids (morphine, fentanyl, hydromorphone, oxycodone) and/or magnesium with ketamine to get a synergic improvement in the analgesia

TABLE 4 Delphi agreement

Level	Strong for	For	Weak against	Strong against
Utility, advantages and effectiveness	Neuropathic pain Evaluation of effectiveness at 1 month	Good to moderate utility in all listed situations or diseases 26 to 50% patients with positive reports in CNP, PNP, opioid withdrawal, palliative care, depression, CRPS and sensitization situations		
Adverse events and deleterious aspects	No deleterious effects in CNP, PNP, opioid withdrawal, palliative care, CRPS and nociceptive pain	Adverse events absent or <3%	Depression	
Administration	IV infusion 0.5–0.9 mg/kg/d Hospital in- or out-patient	4 days Quarterly	IV bolus +IV infusion; SC; PO	SC +IV bolus; SC +IV infusion; SC +IV bolus +IV infusion; SC +PO; intranasal
Concomitant treatments	Combination with non- pharmacological treatment	Good combination with weak and strong opioids, magnesium	Low relevance of combination with paracetamol, NSAIDs, nefopam, lidocaine (IV)	No relevance of combination with oxygen, nitrous oxide, setron, amantadine

was described as ‘Good’. Ketamine associated with weak opioids (codeine, dihydrocodeine and tramadol) was considered as ‘Average’ while the association with paracetamol, NSAIDs or nefopam was ‘Weak’. Experts concluded that many associations of drugs should not be recommended (oxygen, nitrous oxide, setrons and amantadine). Furthermore, 78.6% of experts agreed about an ‘Excellent combination with non-pharmacological treatment’ (acupuncture, physiotherapy, hypnosis, tens, etc.) (Table 3).

3.4.2 | Descriptive data

Experts declared to prescribe ‘Always’ or ‘Most of the times’ analgesics or co-analgesics in combination with ketamine. However, they also declared ketamine could be used to diminish opioids especially in sensitization situations and opioid withdrawal and more moderately in other situations/diseases (Table S1).

4 | DISCUSSION

The aim of this Delphi survey was to identify the beneficial and deleterious aspects of ketamine administration in order to reach a consensus on ketamine administration in chronic pain. It also aimed to establish which medical care was used in this context by the convergence of a maximum of evaluated items. The retention of respondents was excellent during the exercise and was considered as robust (The Delphi Technique in Nursing and Health Research | Wiley (s. d.), 2011), with 87.5% of the original panel taking part in all four rounds. Of the initial 96 items, expert agreement was achieved for 78 items (Tables 3 and 4), with only 18 items that remained controversial while descriptive data were found in Table S1.

4.1 | Utility, advantages and effectiveness

Based on responses obtained from all Delphi rounds, ketamine presents good to moderate utility in all diseases/situations proposed in the survey with a priority to treat neuropathic pain. In order to qualify the interpretation of these results, we relied on the comments made by the experts throughout the trial. Ketamine would therefore be more useful in PNP, CNP, opioid withdrawal, palliative care and depression. Very little literature has focussed on the effect of ketamine on depression as a comorbidity of other pathologies (Jafarinia et al., 2016) while it is better known for treating major depressive disorders refractory to classical

antidepressants (Corrigan & Pickering, 2019). The utility of ketamine is estimated to be moderate in fibromyalgia (nociceptive pain), CRPS, nociceptive pain and sensitization situations. Otherwise, 26 to 50% patients report in favour of ketamine treatment in most described diseases or situations. The distribution of percentages remains consistent with previously estimated utility. Indeed, 40 to 50% patients with positive report would be reported with CNP, opioid withdrawal or depression and 30% patients with CRPS or sensitization situations. In this context, experts agreed on the key role of multidisciplinary management when ketamine is administered (Colloca et al., 2017; Thieme et al., 2017). Sensitization situations including several pathologies (irritable bowel, painful bladder, temporomandibular dysfunction, chronic headache) would deserve to be further analysed individually. In the American recommendations (Cohen et al., 2018), only CRPS presents a moderate evidence to support improvement for up to 12 weeks (Grade B) while other pain conditions show no evidence for immediate improvement (Grade D). Furthermore, Cohen et al. recommend in addition to satisfaction a decrease in pain score $\geq 30\%$ (Grade C recommendations). A recent survey on CRPS reported a variable response in the duration of pain relief (1–10 days in 25% of responders; 1–12 weeks in 33% of responders; 1–6 months in 42% of responders) (Xu et al., 2019). A variability in the responses is observed in FM patients linked to possible ‘responders’ or ‘patients sensitive’ to treatment (Ablin et al., 2016; Hoskin et al., 2018, Corrigan, 2021).

4.2 | Adverse events and deleterious aspects

Considering the potential risks of ketamine, the low frequency of reported adverse events is a positive point (Orhurhu et al., 2021; Peltoniemi et al., 2016). None of the presented diseases or situations appears to have a greater frequency of adverse events occurrence than the others. Less than 3% of patients have headache, bad trip, addiction or psychodysleptic effects. However, resources remain available to doctors to avoid these effects. Discontinuing the infusion allows the disappearance of headache, which is often transient but can be relieved by paracetamol, NSAIDs or oxygen if persisting. In parallel, a low dosage allows to limit the occurrence of addiction, bad trip and psychodysleptic effects (Morgan et al., 2009; Pushparaj and Bhatia, 2020). In this context, it would have been interesting to discuss about clonidine used before and after each ketamine infusion to optimize the neuropathic pain-relieving action of NDMA receptors blockers (Schwartzman et al.,

2011). The rest of the adverse events differs slightly with a downward trend for a few of them such as aggravation of pain, interstitial cystitis, liver injury, constipation or even vein inflammation. Finally, experts believe that no deleterious effect can be attributed to the administration of ketamine in CRPS, CNP, PNP, nociceptive pain, opioid withdrawal and palliative care. Only ketamine when used in patients with depression is weakly deleterious although studies provide evidence of its robust antidepressant effects especially in severe primary depression and not in the context of pain (Miller et al., 2014; Sanacora et al., 2017). In fact, too frequent infusions could lead to a greater risk of dependence (Wilkinson & Sanacora, 2017) which is not enough evoked in the literature although it is a real public health problem. In this context, a collaboration with a psychiatrist may help to detect addictive profiles. The American recommendations (Cohen et al., 2018) describe relative contraindications to ketamine especially concerning poorly controlled cardiovascular disease, pregnancy, active psychosis (Grade B) and moderate to severe hepatic disease or active substance abuse (Grade C). Xu et al. presented similar results to our survey with an incidence of most adverse events less than 5% in CRPS. The post-infusion monitoring according to inpatient therapy (follow-up of 6 hours) or outpatient therapy (follow-up to 60 min) in order to quickly treat any occurrence of adverse event was also discussed.

4.3 | Methods of administration

The mode of administration, the dose, the number of days of treatment are undoubtedly the most controversial subjects in view of the absence of recommendations or guidelines in this context (Cohen et al., 2018), although a reference protocol was described for CRPS patient recently (Xu et al., 2019). Experts in our survey consider that it would be preferable to use ‘IV infusion’ and to proscribe any combination of different routes of administration (‘SC +IV bolus’, ‘SC +PO’, etc.). The intranasal route was also proscribed by the experts due to the higher risk of addiction related on a peak of plasmatic concentration and an easier route of administration. Some routes such as ‘SC’ or ‘PO’ would be poorly recommended or under very specific conditions, especially when the intravenous route is impossible. ‘SC’ and ‘PO’ routes require cautiousness because of the relative bioavailability of ketamine and of its potential risk of misuse (Peltoniemi et al., 2016; Siu et al., 2018). In the context of ‘IV infusion’, the dose chosen by the experts would be 0.5 to 0.9 mg/kg/day over a period of 4 days, preferably in hospital as in- or out-patient. Furthermore, the association of ketamine ‘IV bolus +IV

infusion' has not been recommended in our survey because of a higher risk of neuropsychiatric adverse events despite the potential pharmacological interest of this practice. The majority of experts agree that ketamine should not be administered at home because of the lack of surveillance and the potential for adverse events requiring medical monitoring. In addition, a quarterly administration of ketamine would be recommended and adapted according to efficacy, tolerance and patient profile. Finally, experts believe that it would be relevant to evaluate the effectiveness of ketamine on pain 1 month after administration. In the American recommendations (Cohen et al., 2018), a bolus up to 0.35 mg/kg has been recommended with low level of certainty (Grade C) while dosing range of infusion (0.5 to 2 mg/kg per hour, Grade C recommendations) was relatively higher than the one we describe in this Delphi survey. Furthermore, in the survey of Xu et al., an initial rate was proposed to inpatient of 0.15 mg/kg/h with an increase every 2 h of 5-10 mg on 24 h for 3 to 5 days.

4.4 | Concomitant treatments

Chronic pain patients without concomitant pharmacological treatment are seldom (Dale & Stacey, 2016). Among the list of molecules proposed in combination with ketamine, only morphine, some weak opioids (codeine, dihydrocodeine and tramadol) and magnesium would be of interest. The morphine–ketamine combination is to be considered both in terms of opioid withdrawal and in the indication of certain types of pain (refractory cancer pain, post-operative pain, etc.) (Bell & Kalso, 2018; Lalanne et al., 2016): vigilance on the potential addictive risk is recommended. Magnesium could have an interesting additive effect that needs to be studied (Delage et al., 2017; Pickering et al., 2020). Other listed molecules do not have a real relevance for combination with ketamine including paracetamol, NSAIDs and nefopam. However, paracetamol and NSAIDs would be effective for the treatment of ketamine-induced headache with a higher valence of NSAIDs in the control of acute inflammation (Theken, 2018). Finally, experts agree on the importance of using non-pharmacological treatments (acupuncture, physiotherapy, hypnosis, tens, sporting activity, etc.) for comprehensive multidisciplinary care (Andrade et al., 2018; Hassett & Williams, 2011).

4.5 | No consensus

A small number of items did not reach a consensus of views in this Delphi study, including the low deleterious effects of ketamine in fibromyalgia and sensitization situations.

In this context, deleterious aspects would be reported only with inadequate monitoring and too large doses (Maher et al., 2017). Psychological vulnerability associated with fibromyalgia and potential addiction profiles must be taken into account in the therapeutic strategy (Lichtenstein et al., 2018). The percentage of 40% patients with positive report in fibromyalgia is also controversial and reflects again the concept of 'responder' as well as the difficulty in isolating the effect of ketamine alone when management is multimodal (Häuser et al., 2017). The percentage of 30% patients with a positive report in nociceptive pain is also controversial and depends on the aetiology. The priority ranking of treatments for the pathologies or situations proposed may not have shown a consensual response, but nevertheless brings interesting information. We may suggest a ranking trend as follows: 1/neuropathic pain; 2/prevention of post-operative pain, opioid withdrawal, CRPS, cancer; 3/fibromyalgia, sensitization situations, pelvic pain; 4/ back pain and headache. Regarding the method of administration, 'IV bolus' is preferred intraoperatively or in the context of nociceptive pain relating to care but rarely used alone. Finally, a consensus is almost reached for a 4 days hospital stay, intrinsically linked with the duration of administration of ketamine (see Table S2, which illustrates items without consensual answer).

4.6 | Benefits and limitations

The Delphi method is widely used in the medical field for informing clinical decision making in situations where no recommendations exist (de Meyrick, 2003; Powell, 2003), like for the use of ketamine in chronic pain. The overall results of this study must be interpreted in light of a number of methodological limitations. First, there are no guidelines for objectively defining and selecting experts participating in a Delphi method. The credibility of the expertise then rests entirely on the skills considered as relevant. Therefore, our panel of experts may present differences in terms of place of practice, specialty, patients, painful conditions, causing bias in the responses. Secondly, only clinicians using ketamine in their practice were included in our survey and not clinicians who may have used ketamine previously but had decided not to continue with this treatment. It is important to note that the questionnaire was built by two ketamine-experienced clinicians; it is possible that the survey would have been more relevant if more clinicians had been involved in the development of the survey, but the questionnaire as it is covers all aspects of interest for ketamine use. It might be a limiting factor of the study that the survey was not timed. It would also be necessary to further explore the infusion time (continuous

24/24 h, 6/24 h, etc.), the possibility of progressive doses or even the practice of consecutive/discontinuous days (4 consecutive days, 1 day / month for 4 months, etc.). It is important to note that the infusion time may have an impact on the occurrence of adverse events; this could thus explain the low occurrence of headache, bad trip, addiction or psychodysleptic effects as reported by experts. Finally, another limitation inherent to the Delphi method described by Cook et al. mentions the 'stand-alone principle' (Cook et al., 2005). This highlights the fact of limiting the request of the level of agreement between experts for each variable independently when in fact the expert must rely on the basis of the co-existence (and/or relative absence) of clusters of specific symptoms and signs.

5 | CONCLUSION

This Delphi survey in chronic pain reached agreement on four main aspects: (1) Priority to treat neuropathic pain with evaluation of effectiveness at 1 month; (2) No deleterious effects in the majority of listed diseases/situations with the absence or <3% of suggested adverse events; (3) 0.5–0.9 mg/kg/d IV infusion; (4) Combination with non-pharmacological treatment. The study proposed several indicators on the benefit-risk balance of ketamine in various indications and established a consensus of pain specialists on the use of ketamine, thus providing a basis for future clinical trials.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

MV made substantial contributions to conception and design of the article, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published. **TR** made substantial contributions to the acquisition of data conception, design of the article and final approval of the version to be published. **DC** made substantial contributions to the acquisition of data, revising the article critically for important intellectual content, final approval of the version to be published. **IC** made substantial contributions to data interpretation, revising the article critically for important intellectual content, final approval of the version to be published. **GP** made substantial contributions to conception and design

of the article, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published.

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