Clinical Pain Research

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Ketamine therapy for chronic pain in The Netherlands: a nationwide survey

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Abstract

Objectives: Ketamine is used to treat chronic refractory pain. However, there are no scientific guidelines for ketamine use in the Netherlands. The aim of this survey was to provide an overview of the use of ketamine for chronic pain in the Netherlands.
Methods: All pain clinics in the Netherlands were contacted. A digital survey, available from June 2019 to January 2020, was sent to 68 pain clinics. The survey was completed by one pain physician as a representative of the entire pain department. The survey included questions about ketamine treatment indications, administration, dose, duration, treatment repetition and the inpatient or outpatient setting.
Results: The survey was completed by 51 pain clinics (75.0%). Thirty-one clinics used ketamine for chronic pain treatment. The most common indication was Complex Regional Pain Syndrome (83.9%). Pain clinics administered ketamine via intravenous infusions (96.8%), iontophoresis (61.3%), subcutaneous (3.2%) or oral administration (3.2%). Intravenous ketamine treatment was offered in an inpatient setting in 14 pain clinics, in both an inpatient and outpatient setting in 11 pain clinics and in six pain clinics in an outpatient setting. In the outpatient setting, the median starting dose was 5 mg/h (IQR=17.5–5). The median maximum dose was 27.5 mg/h (IQR=100–11.9). The median infusion duration was 6 h (IQR=8–4). In the inpatient setting, the median starting dose was 5 mg/h (IQR=5–1.5) and the median maximum dose was 25 mg/h (IQR=25–14). Patients were admitted to hospital for a median of 4 days (IQR=5–1).
Conclusions: The results of this Dutch nationwide survey study show that there are heterogeneous treatment protocols with different indications, treatment setting and dosing regimen for the treatment of chronic pain with ketamine. This study encourages the formulation of a broader consensus and the development of evidence based guidelines for ketamine treatment.

Keywords: chronic pain; inpatient/outpatient setting; ketamine; treatment indications.

Introduction

Chronic pain affects 20% of adults in Europe and burdens their daily lives with functional impairment, distress and demoralization [1, 2]. Untreated chronic pain is a major source of suffering for the individual, and creates a socioeconomic burden for health care systems and society in general [1, 3–5]. In addition to these concerns, chronic pain remains challenging to treat due to its variable clinical course and complex pathophysiology. Pain therapies that target mechanisms responsible for pain are gaining popularity [6]. Despite advances in the understanding of pain mechanisms, the search for an ideal individually tailored pain treatment continues.

New insights in the pharmacological profile of ketamine gives this drug a potential place in the treatment arsenal for chronic pain [7, 8]. Ketamine is a dissociative anesthetic agent that has analgesic, psychomimetic, anti-inflammatory and anti-depressant effects trough interaction with multiple receptors [9–11]. The most important effect of ketamine is effectuated through its antagonistic action on the N-methyl-D-aspartate (NMDA) receptor [12–14]. The NMDA receptor plays an important role in the development of neuroplastic changes in chronic pain, such as wind-up and central sensitization [8, 15–17]. These neuroplastic changes can result in spontaneous pain as well as allodynia or hyperalgesia to nociceptive stimuli

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[8, 15, 18]. To treat these symptoms in chronic pain patients, ketamine can be administered to block or attenuate the wind-up phenomenon and central sensitization [8, 15, 19].

Because of these new insights, the use of ketamine as a treatment in chronic pain has gained interest in both research and the clinical setting [19]. Ketamine has been used for multiple chronic pain conditions after conventional therapies have failed. Examples of such conditions include spinal cord injury pain, phantom limb pain, fibromyalgia, cancer pain, ischemic pain, migraine, lower back pain and Complex Regional Pain Syndrome (CRPS) [19, 20]. The efficacy of ketamine in chronic pain has been studied in several articles. These articles reported very low to moderate quality of evidence for the efficacy of ketamine in chronic pain [19, 21–23]. The highest evidence for ketamine infusions has been found for treatment of CRPS [19, 24].

In the Netherlands, there is no consensus on the use of ketamine in chronic pain. The only guideline currently incorporating ketamine treatment in the Netherlands is the Dutch guideline for CRPS [25]: Ketamine is recommended in patients with treatment-resistant CRPS with pain scores of ≥7 on an 11-point Numeric Rating Scale (NRS) [25]. There is no general consensus yet on dosage and administration protocol in the Netherlands. Unfortunately, CRPS and chronic pain literature contains a wide range of ketamine dosing regimens with the result that clinical protocols on dosage and administration are very heterogeneous [21, 24]. In response to the lack of guidelines for appropriate ketamine use, an expert consensus statement of ketamine in chronic pain has recently been published in the United States of America (US) [19]. Such a guideline would also be of value in the Netherlands. However, in order to develop Dutch consensus guidelines, the first step is to evaluate the current use of ketamine for chronic pain in the Netherlands.

Hence, the aim of this study was to evaluate the clinical use of ketamine in chronic pain in the Netherlands and to compare the obtained information with relevant international literature. To this end, we conducted a nationwide digital survey of clinical ketamine protocols in Dutch pain clinics.

Methods

Ethical considerations

Based on current Dutch medical ethical regulations, no institutional review board approval was necessary for this survey.

Data collection

To assess the different protocols used for ketamine treatment for chronic pain in the Netherlands, all pain clinics were primarily approached by phone with the request to grant permission to send the survey. A structured digital survey was designed. The survey was sent by e-mail between June and July 2019 to the pain clinics that agreed to participate. Only one pain physician per approached clinic was required to complete the survey. In case of multiple respondents from one pain clinic, only the answers from the first respondent were analyzed. The survey could be completed from June 2019 to January 2020. Data were digitally processed in Google Forms.

Elements of digital survey

Pain clinics were asked what their treatment indications were for ketamine and what the route of administration was. In addition, they were asked whether they prescribed the enantiomer of S-ketamine, R-ketamine or the racemic mixture of R- and S-ketamine. If there was a clinical protocol for ketamine treatment, pain clinics were asked whether the protocol was based on expert opinion and/or on empirical evidence.

Pain clinics that did not use ketamine for chronic pain were asked about the reason(s) for not prescribing ketamine and whether patients were referred to other institutions that do prescribe ketamine. If the clinic prescribed the treatment in the past, they were asked about the treatment indications. In addition, the reasons for stopping ketamine treatment were asked.

In the survey, a distinction was made between inpatient and outpatient intravenous ketamine treatment. For both the inpatient and outpatient treatment, the survey included questions about dosage and duration of the therapy. The digital survey took into account various elements of dosing regimens to facilitate analysis. It also took into account the units ketamine was administered in: mg/h, mg/kg or mg/kg/h.

Statistical methods

Descriptive statistics were used to determine the frequency of the outcome parameters and to describe measures of central tendency and of variability, dependent on the shape of their distribution. The Shapiro-Wilk test was used to analyze whether continuous parameters were normally distributed. Statistical analyses were performed using IBM SPSS version 25.0.

Results

A total of 68 pain clinics were contacted by telephone and were sent the digital survey. The digital survey was completed by 51 pain clinics (75.0%). Of these 51 pain clinics, 31 (60.8%) used ketamine for chronic pain treatment. Two pain clinics had the survey completed by two pain physicians. Only the answers of the first respondent of the pain clinics were included in the analysis. Figure 1 shows the flowchart of the institutions examined.

Twenty pain clinics (39.2%) did not use ketamine for chronic pain treatment. Five of the 20 pain clinics reported that the department used ketamine in the past to

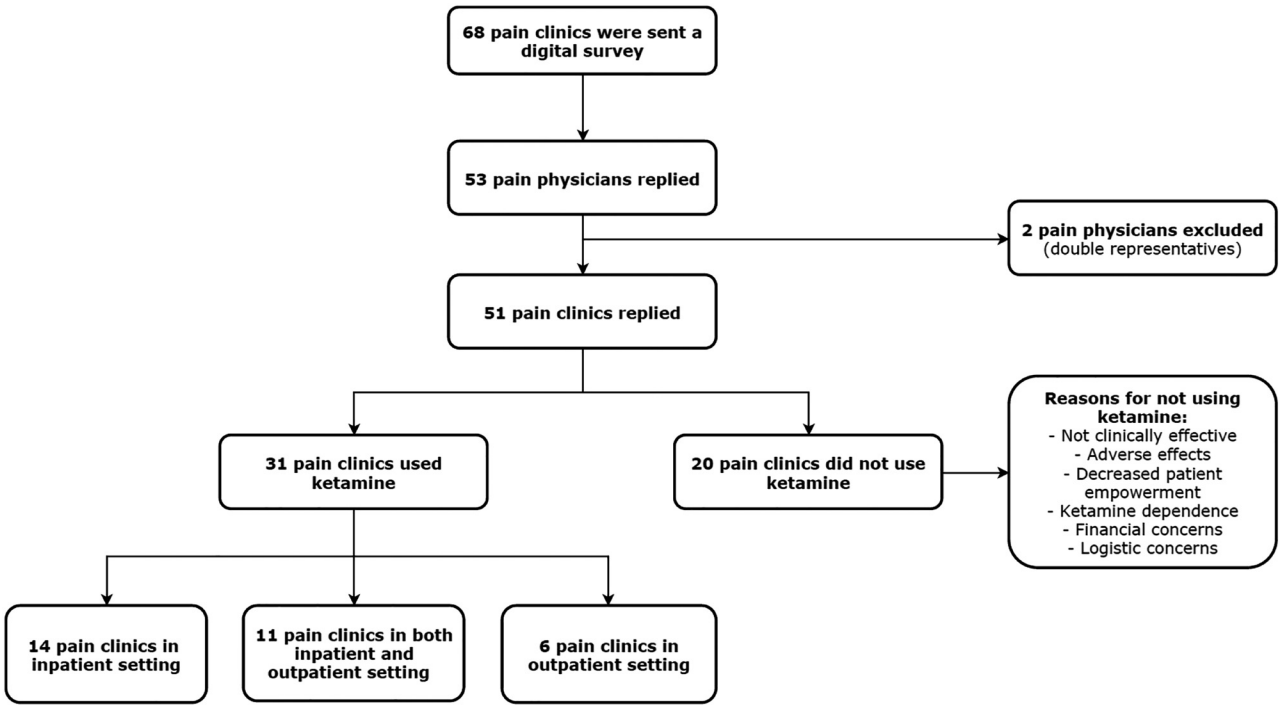

Figure 1: Flowchart of pain clinics surveyed.

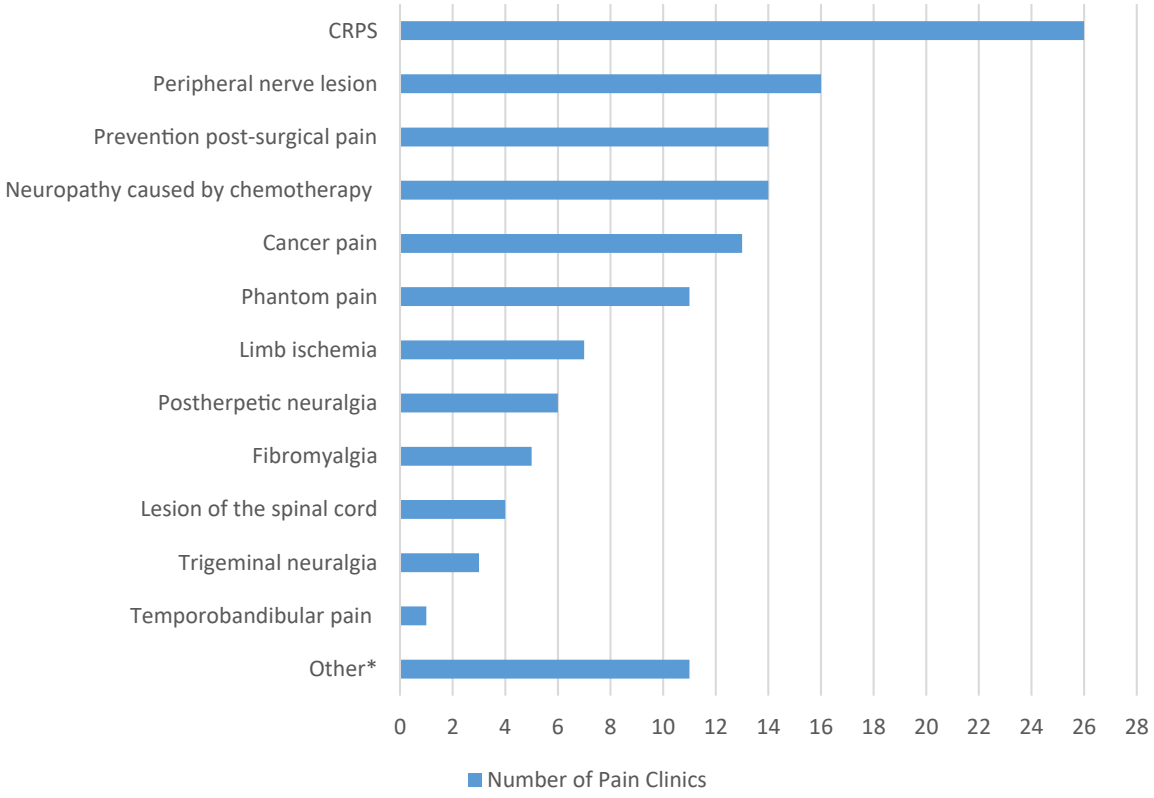

Figure 2: Indications for ketamine treatment (31 pain clinics).
*Other reported indications: Failed back surgery syndrome (FBSS), polyneuropathy, diabetic neuropathy, monoclonal gammapathy of undetermined significance (MGUS), chronic idiopathic axonal polyneuropathy (CIAP), neuralgia, post-surgical pain, suspicion of central sensitization, visceral pain, severe neuropathic pain. Abbreviations: CRPS, Complex regional pain syndrome.

treat chronic pain. The most commonly reported reasons for discontinuing the ketamine treatment were prominent adverse effects, no clinically effective response to treatment and logistical and financial concerns, such as not enough eligible patients and high hospital costs. The former indications for ketamine prescription were CRPS, prevention of post-surgical pain, and cancer pain. Two pain clinics that used ketamine in the past replied that they refer their patients to other hospitals for ketamine treatment if needed.

In the 31 clinics that prescribed ketamine for chronic pain patients, ketamine was used for various indications as shown in Figure 2. Twenty-six clinics (83.9%) used ketamine to treat CRPS. Pain clinics prescribed ketamine for a median of 3 (IQR=5–2) indications. All clinics prescribed the enantiomer S-ketamine. None of them used the racemic mixture of R- and S-ketamine. The most commonly reported route of ketamine administration was intravenous administration (96.8%). An overview of used routes of administration is shown in Table 2.

Of the 31 pain clinics, in 18 clinics (58.1%) the protocol was based on expert opinion and in 10 (32.3%) on scientific literature [19, 26–33]. In 2 clinics (6.5%) the protocol was based on both scientific literature and expert opinion. The answer was missing from one clinic (3.2%).

A total of 11 (35.5%) of the 31 pain clinics offered intravenous ketamine in both inpatient and outpatient setting. Fourteen clinics (45.2%) offered ketamine in the inpatient setting and six clinics (19.4%) in the outpatient setting.

Unfortunately, of the clinics using both inpatient and outpatient ketamine infusions, data were only available from the outpatient setting. This was due to a glitch in the survey that was only noticed after the inclusion period ended and the data had already been collected.

Outpatient setting

In total, 17 clinics offered intravenous ketamine treatment in the outpatient setting.

Treatment duration

In 15 of the 17 pain clinics the median ketamine infusion time in an outpatient setting was 6 h (IQR=8–4). Data on infusion times were missing from two pain clinics.

In 11 of the 17 pain clinics (64.7%), the ketamine treatment was a one-day treatment. In 3 pain clinics (17.6%) the ketamine treatment was given over the course of several days. Two pain clinics (11.8%) offered both ketamine treatments: over the course of several days and one-day ketamine treatments. Information about the duration of treatment was missing from one clinic (5.9%). Data on re-treatment were not available.

Dosing regimen

In 13 of the 17 clinics intravenous ketamine treatment was started at a median dose of 5.0 mg/h (IQR=17.5–5). In 10 clinics the median maximum dose in mg/h was 27.5 mg/h (IQR=100–11.9). Four clinics administered ketamine on a mg/kg dosing schedule. Two pain clinics reported a starting dose of 0.1 mg/kg and the other two pain clinics reported a starting dose of 2.0 mg/kg. The maximum reported doses were 0.2, 0.5, 3.0 and 4.0 mg/kg. Table 1 shows the ketamine dosages reported in an outpatient setting. Two pain clinics reported that there was no specific maximum dose, but the dose was reduced when adverse effects of ketamine were observed (Table 2).

Twelve pain clinics (70.6%) of the 17 pain clinics increased the ketamine dose during the ketamine infusion.

Table 1: Ketamine dosages reported in the survey.

		Units	Median (IQR)	Number of responders
Outpatient setting (n=17)				
	Starting dose	Mg/h	5 (17.5–5)	13
	Maximum dose	Mg/h	27.5 (100–11.9)	10
	Treatment duration	Hours	6 (8–4)	15
	Interval between ketamine treatments	Months	–	–
Inpatient setting (n=14)				
	Starting dose	Mg/h	5 (5–4.3)	12
	Maximum dose	Mg/h	25 (25–14)	11
	Treatment duration	Days	4 (5–1)	14
	Interval between ketamine treatments	Months	4 (6–3)	13

IQR, Interquartile range; mg, milligram; h, hour.

Table 2: Routes of ketamine administration.

Route of ketamine administration	Number of pain clinics (percentage) n=31
Intravenous	30 (96.8%)
Iontophoretic	19 (61.3%)
Subcutaneous	1 (3.2%)
Oral	1 (3.2%)

Four pain clinics (23.5%) increased the ketamine dose in some of their patients. The starting doses of these four pain clinics were: 0.1 mg/kg, 2.0 mg/kg, 5 mg/h and 75 mg/h. One pain clinic (5.9%) did not increase the ketamine dose during the infusion and had a starting dose of 25 mg/h.

Inpatient setting

As mentioned in the first paragraph of our results, of the clinics offering both outpatient and inpatient infusions, unfortunately information about the inpatient infusion was missing and could not be included in the analysis. Therefore, only the data from the 14 clinics offering solely inpatient infusions were available for analysis.

Treatment duration and treatment repetition

Patients were admitted to the hospital for an inpatient ketamine treatment for a median of 4 days (IQR=5–1). Thirteen of the 14 pain clinics repeated the ketamine treatment in the future if necessary. Data on repeat treatments were missing from one pain clinic. The median time interval between ketamine treatments was 4 months (IQR=6–3). To repeat ketamine treatment, there had to be a positive result in the previous treatment. In all 13 pain clinics, pain reduction after treatment was needed to repeat the ketamine treatment. Six clinics (46.2%) required improvement in physical functionality and six clinics (46.2%) a reduction of other pain medication. In 8 clinics (61.5%), a positive experience of the ketamine treatment on pain, as reported by the patient, was sufficient to warrant repeat ketamine treatment.

Dosing regimen

The median starting dose in 12 clinics was 5 mg/h (IQR=5–4.3). When the dose was increased during the infusion, the median dose increment was 2.0 mg/h (IQR=5–1.5). In 11 pain clinics the median maximum dose was 25 mg/h (IQR=25–14).

Two pain clinics administered ketamine on a mg/kg/h dosing schedule. One pain clinic reported a starting dose of 0.5 mg/kg/h and the other pain clinic reported a starting dose of 7.0 mg/kg/h. One pain clinic gradually increased the dose by 5 mg/kg/h in order to achieve pain relief. The two pain clinics reported a maximum dose of 30 mg/kg/h and 50 mg/kg/h, respectively. See Table 1 for a summary of ketamine dosages reported in the survey.

Eleven pain clinics increased ketamine dose during the infusion. Three pain clinics did not change the starting dose during the infusion. Of these three pain clinics, two clinics reported a starting dose of 5.0 mg/h and one clinic reported a starting dose of 0.5 mg/kg.

Definition of an effective pain reduction

Different definitions of effective pain reduction were used in the 14 clinics for which data were available on this subject. In 7 pain clinics (50.0%), a reduction of two points on Numerical Rating Scale (NRS) was cited as effective pain reduction. In 6 pain clinics (42.3%) NRS reduction of three or more was cited as effective pain reduction. Finally, one clinic (7.1%) reported that there was no consensus in the department on what an effective NRS reduction is.

Monitoring of vital signs

Various monitoring methods were used during inpatient ketamine treatments. Three (21.4%) of the 14 pain clinics had continuous vital signs monitoring. Nine pain clinics (64.3%) measured vital signs several times a day. In 1 clinic (7.1%), vital signs were measured at the start and at the end of therapy. Six pain clinics (42.9%) monitored respiratory rate. Fourteen pain clinics (100%) monitored blood pressure. Thirteen pain clinics (92.9%) monitored the pulse rate. Six pain clinics (42.9%) monitored body temperature and two pain clinics (14.3%) specifically mentioned monitoring the oxygen saturation by pulse oximetry.

Discussion

This study created an overview of current clinical practice of ketamine treatment for chronic pain in the Netherlands. It shows a wide variation in ketamine treatment indications, route of administration, dosing regimen, safety measures and treatment repetition.

For pain clinics in the Netherlands, the most common indication for ketamine treatment is CRPS. This is in line with reported positive results in the literature of ketamine treatment in CRPS [21, 24]. Specifically, the systematic review by

Zhao et al. concluded that intravenous ketamine therapy for CRPS can provide effective pain reduction for less than 3 months [24]. Of note were the high heterogeneity across included studies and publication bias, which support the need for guidelines. Besides CRPS, this survey showed that ketamine was administered for other indications. Although the US guidelines concluded that there is moderate evidence supporting ketamine infusions in CRPS, they found no evidence that supports ketamine treatment for intermediate or long-term pain improvements in other pain syndromes [19].

This survey showed that most pain clinics administered ketamine intravenously. All ketamine infusions were prescribed in the S-isomer form. Pharmacological literature shows that S-ketamine possesses respectively 2 and 4 times stronger anti-nociceptive effects than R-ketamine and racemic ketamine [34]. Furthermore, the pharmacological potency depends also on the bioavailability of the different routes of administration. The advantage of the intravenous route of administration is that it avoids first-pass metabolism in the liver. A disadvantage of the intravenous S-ketamine is the invasive route of administration. However, S-ketamine infusions are used as a last resort therapy for severely affected therapy-refractory CRPS patients. In these cases the benefits after therapy could outweigh and justify the risks of this treatment.

Oral and subcutaneous S-ketamine were used sporadically in the Netherlands. While evidence for subcutaneous ketamine is limited, it may be beneficial in refractory cancer pain and chronic nonmalignant pain [20, 22, 35]. The very scarce use of oral ketamine in Dutch pain clinics might be based on the conclusions of Blonk and colleagues that oral ketamine should not be used in routine practice because of its poor safety profile, low bioavailability of approximately 16% and lack of efficacy [36]. This is in line with results of a study in France, where oral ketamine was only prescribed by 13% of the surveyed pain physicians [37].

More than half of the clinics (58.1%) in this survey prescribed ketamine via iontophoresis, although clear evidence supporting this administration route is lacking. In the study of Vranken et al., ketamine was administered to patients with intractable central pain, but this did not result in pain relief after 1 week [38]. However, the scores evaluating quality of life and health status improved significantly after 1 week [38].

In the outpatient setting, the median infusion time of 6 h in the Netherlands was relatively long. A study on ketamine infusion for chronic pain in South Korea showed that all 23 included outpatient institutions used infusion durations between 1 and 3 h [39]. In addition, Xu et al. conducted an international survey on intravenous ketamine use in CRPS and in this study the most commonly reported infusion duration was 4 h [40].

In the outpatient setting, the median starting dose was 5 mg/h and the median maximum dose was 27.5 mg/h in the Netherlands. In the South Korean study, 70% of the institutions used a maintenance dose of 35–70 mg/h normalized to a 70 kg patient (0.5–1.0 mg/kg/h) [39]. In Xu et al., more than half (55%) of respondents used an infusion rate of 2.2–11.7 mg/h normalized to a 70 kg patient (0.75–4 mg/kg/day) [40]. The ketamine dose used in the Netherlands was thus lower than in South Korea, but generally met the dose range of Xu and colleagues. The US guidelines suggested to start with a single, outpatient infusion with a minimum dose of 80 mg with an infusion time of >2 h [19].

In the inpatient setting, the median time of hospitalization was 4 days with a median starting dose of 5 mg/h and a median maximum dose of 25 mg/h. While this dosing regimen is generally in line with studies on which some inpatient protocols have been based [27, 29, 30], this survey showed a wide range of starting and maximum doses. A French ketamine study also showed wide inpatient dose ranges prescribed for chronic pain [37]. The dose varied from 0.1 to 84.0 mg/h normalized to a 70 kg patient (0.001–1.2 mg/kg/h) and infusion duration ranged from 2 to 336 h [37]. Xu et al. reported inpatient infusions ranging from 1.0 to 14.6 mg/h normalized to a 70 kg patient (0.35–5.0 mg/kg/day) with duration of 3–5 days [40]. Although variation between clinics exists, the results of Xu and colleagues generally correspond to the treatment duration and ketamine dosing regimen in the Netherlands.

Previous reviews reported that higher dosages and longer infusion times are associated with greater and prolonged pain reduction [21, 41, 42]. Maher et al. suggested a multi-hour outpatient treatment with multiple clinic visits [41]. Their review recommended a dose between 7 and 35 mg/h normalized to a 70 kg patient (0.1 and 0.5 mg/kg/h) and the longest infusion duration that is logistically feasible [41]. The review by Noppers and colleagues noted that it was unlikely that infusion durations less than 2 h would achieve pain relief for more than 2 days [42]. Infusions longer than 10 h resulted in pain reduction of >50% for more than 2 days with a dose of 16–25 mg/h [42]. Based on these reviews the US guidelines concluded that there is evidence to support higher dosages of ketamine over longer time periods and more frequent administration [19].

These findings support the relatively long infusion time in outpatient clinics in the Netherlands. In addition, although relatively high dosages are proposed in the literature, the dose ranges in our survey roughly meet the recommended ranges of Noppers and Maher et al. [41, 42]. Taking the above into account, reference protocols should be developed for future studies in various pain etiologies for both inpatient and outpatient settings.

The majority of pain clinics monitored the hemodynamic status of patients and measurements were usually taken periodically during the infusion. However, this survey showed large differences between clinics, as some clinics only used vital function measurement prior to ketamine infusion and at discharge, while other clinics used continuous monitoring. The study conducted in France reported use of heart rate (62%), blood pressure (66%) and pulse oximetry monitoring (29%) [37]. Twelve percent did not measure vital parameters [37]. The wide range of ketamine dosage or patient comorbidities could explain different monitoring methods. The US guidelines recommend that the frequency and extent of monitoring should be dependent on comorbidities and periprocedural anomalous vital parameters [19]. Similar protocols, that are used for procedural interventions and monitored anesthetic care, can be used for ketamine infusions for chronic pain [19].

Our survey showed that there is no consensus on the definition of effective pain reduction after ketamine treatment. Most clinics used an NRS reduction of ≥2 to identify effective pain reduction. In Xu et al., most responders used >50% reduction in pain score to define a successful treatment [40]. In search of a benchmark for an effective pain reduction, Farrar et al. concluded that a two-point or 30% reduction in pain is clinically important [43]. The US guidelines recommended considering a positive outcome as ≥30% pain relief [19]. In addition to subjective pain scores, other factors such as quantitative sensory testing, functionality, capability of working and quality of life must be taken into account [19, 44–46]. This survey showed that in some clinics, in addition to pain relief, additional improvement of functionality or reduction of co-medication was needed. More research is needed to develop measurement tools that distinguish successful treatments and aid in the decision to repeat ketamine treatment.

The repetition interval between inpatient ketamine infusions in this study was 4 months. In the outpatient setting, Xu and colleagues reported that most clinics administered ketamine treatments with intervals ranging from a week to a year [40]. In the outpatient study by Anaya et al., the most common repetition interval was 1–3 months [39]. In terms of positive treatment response, the US guidelines consider >3 weeks after a single outpatient infusion and >6 weeks after an inpatient or series of infusions as reasonable guidance criteria [19].

This study has several limitations. First, we encountered missing data in some questions and were therefore unable to include them in the analyses. Data from some inpatient clinics were missing due to a glitch in our survey system. Second, the inpatient clinic questionnaire was more comprehensive than outpatient clinic questionnaire, including questions about monitoring methods, repeat treatment and the definition of an effective pain treatment. Although we paid more attention to these issues in the inpatient group, the questions gave us new insights and should be further explored in outpatient clinics. Third, the survey findings are based on individual physicians as representatives of their pain clinics, which can result in recall bias. Fourth, we did not address the decision to prescribe ketamine in either an inpatient or outpatient setting. Therefore, further research should be done in the form of randomized controlled trials to compare inpatient and outpatient ketamine treatments. Finally, information on adverse effects, patient characteristics and co-medication were not in the scope of this study. Of note, several studies provide extensive information on adverse effects during and after ketamine administration [8, 19, 24, 30, 31].

To our knowledge, this is the first survey study–with a high response rate (75%)–that provides an overview of ketamine treatment for chronic pain in the Netherlands. The strength of this study is that this overview can be used as a basis for developing a guideline on the use of ketamine for chronic pain in the Netherlands.

Conclusion

In conclusion, the majority of pain clinics in the Netherlands use ketamine in the treatment of chronic pain. The results of this national survey show that there are heterogeneous treatment protocols with different indications, treatment settings, dosing regimens and safety measures for the treatment of chronic pain with ketamine. In addition, different definitions of a positive treatment response were used in inpatient clinics. The findings of this study underline the need for a broader consensus in the Netherlands on ketamine use. This is necessary to create evidence based guidelines to optimize ketamine treatment for different chronic pain etiologies.

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