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Efficacy and safety of oral ketamine for the relief of intractable chronic pain: A retrospective 5-year study of 51 patients

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Abstract

Background: This work summarizes the efficiency, failures and adverse effects of oral administration of ketamine at home for intractable pain.
Methods: This 5-year retrospective study involved testing ketamine by intravenous in-hospital administration, then a conversion to an oral route, or oral treatment directly administered at home. The daily intravenous dose was increased by steps of 0.5 mg/kg to attain an effective daily dose of 1.5–3.0 mg/kg. Pain was evaluated on a numeric scale from 0 to 10, and evidence of adverse effects was collected every day. The effective daily dose was delivered orally (three to four intakes). If effective, ketamine was continued for 3 months. Short infusions or direct oral treatment began with a 0.5-mg/kg dose, then the daily ketamine dose was increased in 15- to 20-mg increments.
Results: Among 55 cases (51 patients, neuropathic pain 60%), the mean effective oral dose was 2 mg/kg. Ketamine was effective in 24 patients (44%, mean pain reduction 67 ± 17%), partially effective in 20% (mean pain reduction 30 ± 11%), with a mean opioid sparing of 63 ± 32%, and failure in 22%. Half of the patients experienced adverse effects, but only eight had to stop treatment. For patients with opioid therapy, failure of ketamine was less frequent (7% vs. 36%; $p < 0.02$), with fewer adverse effects (33% vs. 68%; $p < 0.01$).
Conclusions: Pain was reduced or abolished in two-thirds of patients under ketamine therapy; ketamine was effective for patients taking opioids and resulted in few adverse effects.

1. Introduction

Some patients with chronic pain do not respond to the usual analgesic therapies. Some present intractable pain, which is resistant to morphine treatment. Moreover, opioids favour the phenomena of acute and chronic tolerance, termed opioid-induced hyperalgesia (Guignard et al., 2000). These effects, which are dose-dependent, result in part from the involvement of N-methyl-D-aspartate (NMDA) receptors in the central nervous system (Mion and Villevieille, 2013). Hyperactivity of NMDA receptors plays a major role in the genesis of neuropathic pain. Long-term changes in neuronal excitability, which explain the phenomena of allodynia and hyperalgesia, rely in synapses activated by excitatory amino acids. Thus, the NMDA non-competitive channel blocker ketamine may represent a potential therapeutic alternative in many chronic pain conditions (Grande et al., 2008), especially for patients taking opioids, with beneficial effects in the long term (Sigtermans et al., 2010; Patil and Anitescu, 2012).

Ketamine binds to an intrachannel site, decreasing the channel opening time. It decreases 'wind-up', the amplification of the response to repeated stimulation, considered an elementary form of sensitization of the central nervous system (Guirimand et al., 2000). Antagonism of the NMDA receptor is increased if the

What's already known about this topic?
- N-methyl-D-aspartate receptors play a major role in neuropathic pain and opioid-induced hyperalgesia.
- The 'use dependence' explains why the more severe or chronic the pain, the more effective the ketamine analgesic properties.
- There are no official recommendations for the use of ketamine for chronic pain.

What does this study add?
- This study confirms that two-thirds of patients with refractory chronic pain may benefit from ketamine.
- The longer the patients receive an opioid treatment, the more ketamine should be an option.
- We propose 4-h intravenous tests or direct oral titration for ketamine ambulatory oral administration.

channel has been previously opened by glutamate fixation and membrane depolarization. This 'use dependence' explains why the more severe or chronic the pain, the more effective the ketamine analgesic properties (Polomano et al., 2013). Ketamine also acts through descending pain modulation pathways (Niesters et al., 2013) and has anti-inflammatory properties (De Kock et al., 2013). Small ketamine doses improve the mood of depressed patients, a phenomenon that may participate in the analgesic effect in chronic pain (Romero-Sandoval, 2011).

Ketamine may be administered by numerous routes: intravenous (i.v.), intramuscular, subcutaneous, oral (p.o.) and others (e.g., intranasal, sublingual, rectal). Although tests are often made by the i.v. route, the p.o. route is a convenient choice for ambulatory treatment. Despite the promise of ketamine, a recent review of the use of oral ketamine for palliative care could not identify official recommendations for its use (Soto et al., 2012). Reported protocols remain empirical and heterogeneous, which explains the difficulty in analysing the literature. The level of evidence remains low overall (Bell et al., 2003; Jackson et al., 2005; Jost et al, 2010), and most investigations include small numbers of patients ($n < 30$). Finally, the frequency of important side effects may preclude the use of ketamine for chronic pain (Hocking and Cousins, 2003).

For 7 years in our chronic pain centre, cases of intractable pain with failure of conventional treatment have been referred for oral ketamine administration. Here, we summarize the observed efficiency and failure of this treatment and secondary effects that may be encountered with oral ketamine administration in a retrospective study.

2. Methods

This was a 5-year retrospective study (2007–2012) of consecutive patients with intractable chronic pain for which the team in charge for managing pain introduced ketamine as a rescue treatment because of therapeutic impasse.

2.1 Patients

2.1.1 Inclusion criteria

All patients had experienced pain syndromes for several years and the chronic pain was no longer responding to usual treatment. All had been treated in the same pain centre by the same physicians. Some received opioid therapy for non–cancer-related chronic pain; some exhibited no indication for opioid therapy, but in some instances, opioid therapy had been discontinued because of lack of efficacy or because secondary effects outweighed clinical benefit.

The chronic pain syndromes were neuropathic pain (peripheral or central origin), often of post-surgical origin, fibromyalgia, rheumatic pain or miscellaneous conditions such as complex regional pain syndrome or myalgia. Finally, we included some patients receiving high doses of opioids, who were aware of no need to increase their treatment and who were admitted for morphine withdrawal.

All patients who agreed to this alternative therapy had been informed, via a written document, of the potential benefits and side effects of the treatment and ways to mitigate them. The document stipulated that this treatment would be temporary, and that therapeutic de-escalation would follow 1–3 months of treatment.

2.1.2 Exclusion criteria

Most cancer patients were not included because they were not regularly followed in our clinic unless the cancer appeared secondarily and was not the cause of the initial pain. No patients with unbalanced hypertension or psychotic conditions were included.

2.2 Methods

The main goal of the therapeutic programme is to allow patients to take their treatment at home. Ketamine efficacy and tolerance was initially tested by the i.v. route as in-hospital administration, then converted to the oral route, but with time, simpler procedures were adopted. Thus, three procedures have been commonly used (flow chart, Fig. 1):

2.2.1 In-hospital administration

Because ketamine should be administered as prolonged i.v. infusions (4–10 days) (Goldberg et al., 2005) and infusions of

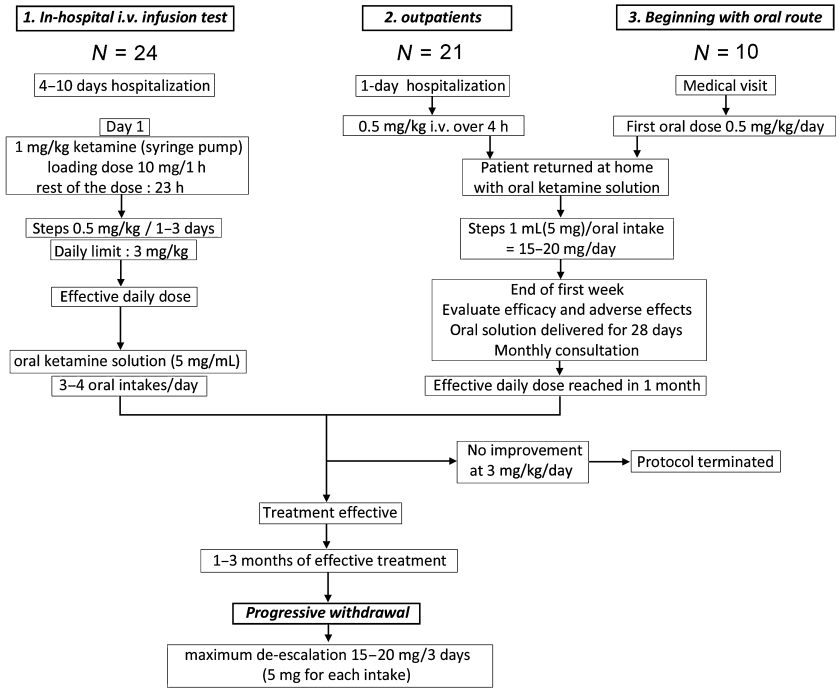

Figure 1 Flow chart describing the three possibilities in ketamine titration protocol (*N* = 55).

shorter duration were not effective in the long term (Noppers et al., 2011b), patients were hospitalized for 10 days at the beginning of the protocol for an i.v. infusion test. The test began with administration by syringe pump of 1 mg/kg ketamine per day (10 mg/mL vial, containing 50 mg racemic ketamine). On the first day, a loading dose consisted of a 1-h continuous infusion of 10 mg. The rest of the daily dose was then delivered during the 23 remaining hours. This daily dose was subsequently increased every 1–3 days, by steps of 0.5 mg/kg to safely attain an effective daily dose of 1.5–3.0 mg/kg.

Data on pain and unwanted effects were collected every day. Pain was evaluated on a numeric scale from 0 to 10. The effective dose was evaluated over 4–10 days. When the effective daily dose had been determined, the same dose was then delivered orally by means of a ketamine solution of 5 mg/mL prepared locally by the hospital pharmacy. Oral intake was divided into three daily doses, or when the patient needed a nightly dose – four daily doses. If the treatment was effective, it was continued for 1–3 months at the full dose, then gradually decreased. Without significant improvement of pain at 3 mg/kg/day, the protocol was terminated.

2.2.2 I.v. administration during 1-day hospitalization for outpatients

Outpatients underwent a more flexible protocol with an infusion of 0.5 mg/kg over 4 h only to test potential side effects. The patient then returned home with the oral ketamine solution and was allowed to increase the dose every day, at steps of 15–20 mg/day up to the daily limit of 3 mg/kg.

2.2.3 Beginning with the oral route

Recently, because of usually good tolerance to the ketamine oral solution, we began initial administration of the oral solution at home at a starting dose of 0.5 mg/kg/day. The first dose is now administered during the medical visit and the patient returns home with the amount of oral ketamine solution needed for 1 week. The patient is allowed to increase each oral intake by steps of 1 mL (i.e., 5 mg for each intake), three to four times daily, which represents a maximum daily escalation of 15–20 mg. The effective daily dose is reached in about 1 month. All patients visit at the end of the first week to evaluate efficacy and adverse effects. The oral solution is then delivered for 28 days and the modalities of follow-up are explained with a monthly consultation. All patients were able to obtain information by phone or email contact.

2.3 Progressive withdrawal

To prevent withdrawal symptoms, which were observed in two patients at the beginning of the protocol, after 1–3 months of effective treatment, the daily dose was progressively lessened with a maximum de-escalation of 15–20 mg (5 mg for each intake) every 3 days.

2.4 Oral ketamine solution

In France, ketamine is an anaesthetic drug intended only for hospital use. Currently, ketamine is not commercially available in oral formulation (McNulty and Hahn, 2012). In some

pain centres, practitioners and hospital pharmacists have developed a protocol whereby an outpatient may receive adequate treatment for 4 weeks. Because ketamine is sometimes used as a 'street' drug, the question of potential abuse remains important and the preparation of ketamine is subjected to regulation. However, whether long-term use for patients with chronic pain produces dependence remains unclear. To ensure its justified prescription, oral ketamine is started only on the recommendation of a palliative medicine consultant or a pain clinic physician. Because oral ketamine is used off-label, every delivery is followed up and registered. Finally, a specific course for delivery that is simple and safe is required for patients who are ambulatory. Prescribers must ensure that they write detailed prescriptions with full information on strength, dosage, route and required quantity. Each prescription cannot exceed 28 days for ambulatory patients. For several years, our hospital has allowed this practice for the benefit of some patients with chronic intractable pain.

Because ketamine is not allowed in community pharmacies, hospital pharmacies prepare, provide, deliver and invoice the treatments. The health care system in France covers the costs of ketamine. The availability of a ready-to-use, standardized solution may contribute to optimal care. In the absence of a specific oral formulation, which is not currently approved, a solution for oral medication can be prepared by the hospital pharmacist from vials of i.v. ketamine diluted with purified water. Ketamine is not available as raw material in pharmaceutical quality.

The chemical stability of compound ketamine and purified water was determined by means of a ultraviolet infrared method: the preparations, stored at 2–8 C, show chemical stability (6 months if the bottle has not been opened and remains protected from the light, and 1 month after opening). As an oral solution, sterility testing was not performed. Because of its chemical stability, a sizeable batch (5 L) of ketamine solution (5 mg/mL) is prepared in advance at the hospital pharmacy, is quantitatively and qualitatively controlled, and is divided into brown bottles. A wide range of five standard doses (50, 75, 300, 625 and 1250 mg) can provide reasonable flexibility to fill each prescription. As well, the solution can be mixed with soda or fruit juice (Lossignol et al., 2005) immediately before swallowing to mask the particularly bitter taste. The ketamine prescription is delivered along with an oral syringe and bottle stoppers for withdrawal of the solution from the bottle. This hospital preparation is reported to the *Agence Nationale de Sécurité du Médicament* in France. In addition, patients are given information leaflets written by the pharmacist in close collaboration with specialists.

2.5 Monitoring and prevention of side effects

With ketamine treatment, the daily dose of opioids was reduced by twofold for all patients receiving high doses of opioids. This dose was then reassessed on a daily basis. Psychic effects (e.g., hallucinations, confusion, malaise) were treated with oral midazolam (2.5 mg on sugar during i.v. infusion) or with haloperidol (for outpatients). Cramps were treated with oral baclofen (3 tablets per day). Liver function was evaluated before ketamine treatment and thereafter on a regular basis (Noppers et al., 2011a). From 2009 onward, patients were informed about the risk of urologic insult.

2.6 Main goals of the study

(1) Pain was evaluated on a numeric scale (0–10) before ketamine treatment and immediately after i.v. infusion. During oral treatment and after ketamine treatment had been stopped, it was evaluated every time a medical consultation was planned. Reduction in pain by >50% was defined as successful response to ketamine. An important improvement in quality of life was also taken into account. If the quality of life had not improved and pain intensity had been reduced by <25%, ketamine treatment was considered a failure.
(2) The de-escalation of opioids was quantified and considered clinically significant when the reduction in opioids dose was >30%.
(3) Definition of responders, nonresponders and partially responders.
Although other studies report global results, such as mean reduction in pain intensity, this way in reporting results is poorly informative because of the wide variation in patient responses. Responders have in most works at least 50% reduction in pain intensity, relief from associated problems (depression, sleep disturbances,) and better ability to work (Moore et al., 2013). That was our definition of ketamine being effective. On the basis of our main goals, reduction in opioid needs was an expected benefit of ketamine, even in case of insufficient pain reduction.

Thus, according to the goals of introducing oral ketamine, the patients were expected to belong to one of four groups:
(1) Effective: mean pain reduction ≥50% and/or quality of life significantly improved;
(2) Partially effective: mean pain reduction 25–50%
(3) Opioid sparing only: mean pain reduction <25%, but opioid dose decreased by at least 30%; and
(4) Failure: mean pain reduction ≤25%, quality of life not improved and opioid dosage not decreased.

2.7 Statistical analysis

Results are reported as mean ± standard deviation or median (interquartile range). Depending on the distribution of the data, means were compared by Student *t*-test or with distribution-free tests (Mann–Whitney or Kruskall–Wallis test, depending on the number of groups). If necessary, continuous data were compared by Pearson correlation analysis. Categorical data were compared by Pearson chi-square test, with appropriate combining of data when expected sample sizes were too small. All tests were two-sided, with $p \leq 0.05$ considered statistically significant. Analysis involved use of StatEl for Microsoft Excel (Ad Science, Paris, France).

Table 1 Characteristics of patients and type of pain by ketamine treatment response.

Patient characteristics	Effective 44% (n = 24)	Partially effective 20% (n = 11)	Opioid sparing only 14% (n = 8)	Failure 22% (n = 12)	Total (n = 55)
Pain lowering on a numeric scale	67 ± 17%	30 ± 11%	6 ± 12%	4 ± 9%	40 ± 33%
Age (years)	47 ± 13	49 ± 11	46 ± 9	45 ± 13	46 ± 12
Sex ratio, M/F, n	13/11	2/9	0/8	3/9	17/34
Body mass index, kg/m^2	25 ± 4	26 ± 5	22 ± 3	26 ± 4	25 ± 4
Type of pain (n)					
Neuropathic	13	7	5	8	33 (60%)
Rheumatologic	6	3	2	2	13 (24%)
Fibromyalgia	2	0	1	2	5 (9%)
Miscellaneous	3	1	0	0	4 (7%)

Data are mean ± standard deviation unless indicated.

3. Results

We could retrieve 55 records of cases from the pain centre database, which corresponded to 51 patients (four patients underwent two separate ketamine treatments). The sex ratio (M/F) was 17/34 (0.5). The mean age was 46 ± 12 years and body mass index 25 ± 4 kg/m. The description of pain types is reported in Table 1.

Among the 55 treatments, the mean reduction in pain with oral ketamine as compared with before treatment was 40 ± 33%. The mean effective oral dose was correlated, but not greatly with dose by weight (145 ± 63 mg vs. 2.03 mg/kg, $p < 0.03$; $R^2 = 0.09$). Data for the median oral dose are in Supporting Information Fig. S1 and median treatment duration in Supporting Information Fig. S2.

According to their response to the treatment, patients were divided in four groups: oral ketamine was effective in 44% (24 patients), partially effective in 20% (11 patients), with opioid sparing without pain reduction in 14% (8 patients), and completely ineffective in 22% (12 patients, Table 1). Overall, in groups 1, 2 and 3, opioid sparing was 62 ± 38% (Supporting Information Table S1).

The groups did not differ in sex ratio, age, body mass index or characteristics of pain (neuropathic vs. other diagnoses) (Table 1); however, the groups did differ in time course of pain reduction with nearly no variation for groups 3 and 4, a transitory reduction for group 2 as long as oral ketamine was administered, and a sustained reduction for group 1 (Fig. 2 , $p < 0.00001$), even when oral ketamine had been stopped. At analysis of the data, among the 24 patients in group 1, five patients had been lost to follow-up, 1 was still receiving ketamine treatment, one was dead and two were relieved of the medical condition that had been the cause of their chronic pain. Among the 15 remaining patients, three (20%) showed no sustained amelioration of their pain after the end of the ketamine treatment, but two (13%) showed >2 months reduction of pain and 10 (67%) showed >6 months reduction.

Among the entire cohort of cases ($n = 55$), pain reduction was correlated with the precocity of introduction of ketamine after the beginning of chronic pain ($p = 0.03$), dose ($p < 0.02$) or duration ($p < 0.05$) of perfusion, taking opioids and duration of oral treatment ($p = 0.003$). However, overall, determination coefficients were weak.

The 4 groups did not differ in delay before beginning ketamine treatment after the onset of chronic pain, therapeutic strategy (i.v. test, short or long, or direct oral route), ketamine dose, adverse effects rate or treatments other than opioids (antidepressants, antiepileptic drugs or other treatments).

In contrast, patients without any opioid treatment during the ketamine challenge showed a 36% failure rate, whereas those receiving opioids showed only a 7% failure rate ($p < 0.02$). This finding was mainly related to the fact that opioid de-escalation with oral ketamine was an expected benefit of oral ketamine. The groups differed by oral treatment duration ($p < 0.0001$) with, of course, continuation of the treatment only when it was effective (Supporting Information Table S1, Online only supplementary material). At the end of treatment when ketamine decreased pain intensity ($p < 0.05$), patients were more often working and less often off work because of disability (Supporting Information Table S2).

About half of the patients (51%) showed adverse effects. Their nature is detailed in Fig. 3. Only in one patient were cramps not relieved by baclofen. Only two patients showed elevated levels of liver enzyme >3 times the normal values before the beginning of ketamine treatment. These patients, included for compassionate reasons, were carefully monitored. Liver disturbances did not deteriorate and progressively returned to normal. In all, eight ketamine treatments

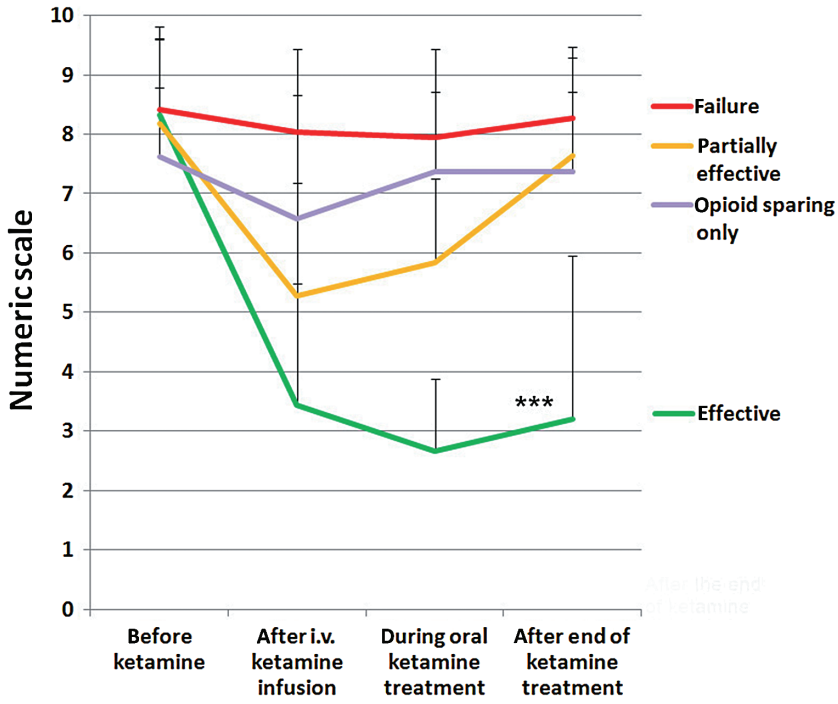

Figure 2 Dynamics of pain, evaluated on a numeric scale, before, during and after the end of ketamine treatment (***compared with the thre other groups: $p < 0.0001$).

had to be stopped because of adverse effects: one case for cystalgia, three cases for headaches, and four cases for psychic effects (hallucinations, malaise, dizziness and sedation). The occurrence of adverse effects was not related to age, body mass index, type of pain, delay in beginning ketamine treatment after the onset of chronic pain, reduction in pain, or dose and duration of oral treatment. In contrast, adverse effects were lower for patients receiving than not receiving opioids (33% vs. 68%, $p < 0.01$; Supporting Information Table S3).

4. Discussion

This retrospective study of 55 cases of oral ambulatory ketamine treatment shows that refractory chronic pain was abolished in 44% of patients; that opioid therapy could be reduced by 62%, on average; and that only 22% of patients did not benefit at all from oral ketamine. Of note, patients receiving opioid therapy tended to benefit from oral ketamine and showed few adverse effects.

As early as 1990, two Japanese teams reported the use of ketamine for treating cancer-associated pain (Kanamaru et al., 1990; Oshima et al., 1990). Four years later, Backonja et al. demonstrated in a double-blind controlled study versus placebo that 0.25 mg/kg i.v. ketamine improved allodynia and hyperalgesia in five of six patients with intractable neuropathic chronic pain (Backonja et al., 1994). As these seminal publications, a large number of papers reported the efficacy of ketamine for intractable pain, but most were case reports (Hoffmann et al., 1994; Knox et al., 1995; Mion et al., 1997; Koulmann et al., 2004) or involved small series (Kiefer et al., 2008; Bredlau et al., 2013a), although some were controlled trials (Mercadante et al., 2000; Mitchell and Fallon, 2002; Noppers et al., 2010). In most papers, ketamine, used as i.v and subcutaneous infusions or oral medication, (Broadley et al., 1996) reduced paroxysmal pain and allodynia when all other therapeutics had failed (Guedj et al., 2007; Azari et al., 2012).

Moreover, since 1998 (Chow et al., 1998), many papers have pointed to ketamine enabling a marked

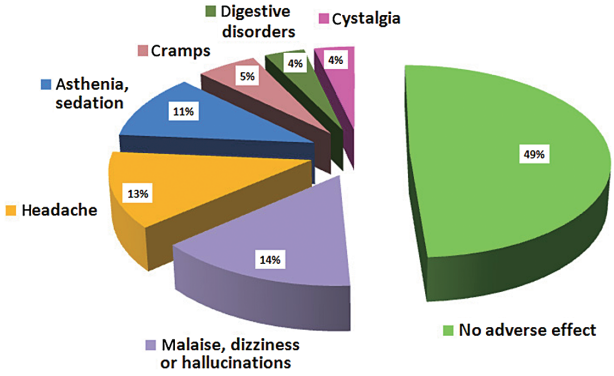

Figure 3 Adverse effects with ketamine treatment in 55 cases.

and sustained reduction in need for opioid therapy for patients that had become refractory to high doses of morphinomimetics (Cherry et al., 1995; Clark and Kalan, 1995; Quinlan, 2012; Barreveld et al., 2013). A synergistic action between ketamine and opioids has been demonstrated in patients with chronic pain. Indeed, NMDA receptor inhibition with ketamine may oppose opioid-induced hyperalgesia and NMDA-related neuropathic pain (McQueen and Baroletti, 2002). Overall, ketamine may represent a therapeutic alternative when other treatments have failed, with a progressive disappearing of central sensitization (Mercadante et al., 2000). Injection of an i.v. dose as low as 2.5 mg may reduce pain refractory to continuous high-dose infusions of morphine. A significant analgesic effect is reported despite a halving of morphine doses, with respiratory benefits (Mercadante, 1996; Koulmann et al., 2004; Lossignol et al., 2005). In 1999, Lauretti et al. showed that 0.5 mg/kg ketamine p.o. every 12 h reduced the required amount of morphine and reduced drowsiness, constipation, nausea and vomiting associated with opioid use (Lauretti et al., 1999).

Ketamine has been reported to be effective against neuropathic pain of central (Devulder et al., 2002) or peripheral origin (Kvarnstrom et al., 2003), such as post-herpetic neuralgia (Eide et al., 1994), pain secondary to multiple sclerosis (Sakai et al., 2004), phantom limb pain (Eichenberger et al., 2008), facial pain (Alvarez et al., 2003), migraines (Afridi et al., 2013) or erythromelalgia (Uchida et al., 2002), and may be useful in complex regional pain syndrome (Correll et al., 2004) and fibromyalgia (Henriksson and Sorensen, 2002). The same effects have been widely observed in cancer patients (Clark and Kalan, 1995; Mercadante et al., 2000; Jackson et al., 2001; Kannan et al., 2002; Bredlau et al., 2013b).

In contrast, Haines and Gaines reported that an oral dose of ketamine improved analgesia in only 3 of 21 patients, only a 14% success rate. The side effects of the molecule limited the utility in almost half of their patients (Haines and Gaines, 1999). More recently, in a controlled trial of 185 subjects, Hardy et al. found that ketamine did not have net clinical benefit when used as an adjunct to opioids for chronic uncontrolled cancer pain. The study, however, was criticized because of a too-short and too-fast ketamine dose escalation, which explains a prohibitive rate of adverse effects (Hardy et al., 2012).

Nonetheless, for more than 600 patients included over 20 years in series or randomized controlled trials (RCTs), the response to ketamine was about 60%. The 'clinical real-world experience' challenges the chronic reluctance of reviews to admit this fact (Jackson et al., 2005; MacKintosh et al., 2012). The Rabben et al. study of 43 patients is in close agreement with our findings: one-third of patients showed permanent response to ketamine, one-third showed transient amelioration and one-third showed no response (Rabben et al., 1999). The Noppers review of 36 RCT reports confirmed that ketamine could persistently (several weeks to more than 3 months) decrease chronic pain (Noppers et al., 2010).

The differences between-response and non-response may be explained by different metabolic pathways (Rabben and Øye, 2001) because metabolites other than norketamine (Malinovsky et al., 1996), namely dehydronorketamine and hydroxynorketamine (Zhao et al., 2012), play a role in neuropathic pain analgesia (Goldberg et al., 2010). Zarate et al. confirmed that response to ketamine or adverse effects may be related to the predominating metabolic pathway (Zarate et al., 2012). Alternatively, with the long duration of pain, hyperalgesia might be due to mechanisms independent of NMDA receptors.

Tests to determine response and non-response are not standardized (Cohen et al., 2009a). Doses range from 5 to 50 mg. One team found a good predictive value (Cohen et al., 2009b) of the response to an i.v. dose of 0.1 mg/kg. Our team began to perform these tests on a 10-day basis, but we are now using more simple schemes with 4-h tests, or even direct oral ambulatory titration. Once the i.v. test has been performed, ketamine treatment is converted to the oral route for prolonged administration. During oral administration of ketamine, active metabolites explain part of the analgesic effects (Mercadante, 1996) because of the hepatic first pass. For this reason too, the oral route is associated with fewer adverse effects (salivation or psychic effects) than the parenteral route (Cherry et al., 1995). Thus, with an oral-administration relay, the proposed doses vary from one-third (Fitzgibbon et al., 2002) to 100% of the parenteral dose. Daily doses of 120–600 mg may be taken in three to five intakes. A recent systematic review proposed to start with unit doses of 0.5 mg/kg; cognitive effects are often minor (Blonk et al., 2010).

Ketamine treatment can often be interrupted by 1–2 weeks; too-short treatments are not effective (Noppers et al., 2011a). A withdrawal period of 2 additional weeks with progressive decreasing doses is usually planned. Apart from this usual scheme, long-term oral ketamine administration, preferentially for compassionate protocols, have been seldom reported for periods ranging from several weeks to more than 1

year (Klepstad et al., 2001; White and Karsli, 2007). Despite the recommendation that ketamine treatment at an effective dose should last no more than 3 months, some of the patients in our series were reluctant to stop their treatment. This situation explains the interquartile interval (25–75%) of 1 and 8 months (Supporting Information Fig. S2). When duration exceeds several months, the risk of toxicity, although described in 'street' users, is of major concern and includes urologic (Smith, 2010; Yiu-Cheung, 2012; Pal et al., 2013), hepatic (Noppers et al., 2011b) or cognitive disturbances (Chan et al., 2013). Some imaging studies also reveal potential brain damage (Wang et al., 2013). Half of our patients did not experience adverse effects, 25% had expected effects observed in most studies (sedation or psychic effects, Fig. 3). Of interest is the reporting of headaches and cramps. Two patients showed hepatic dysfunction before ketamine treatment, and these disturbances did not deteriorate after treatment.

Overall, more than two-thirds of our patients benefited from ketamine treatment. In all, 15 (27%) showed a spectacular functional amelioration (a return to work or resuming a physical activity), and five (9%) benefited from long-lasting opioid withdrawal (several months or longer). Only eight stopped the treatment because of adverse effects.

5. Limitations of the study

This is a retrospective, non-randomized study, so a placebo effect of 10% to 20% cannot be ruled out (Cepeda et al., 2012). However, case reports of patients unaware of the use of ketamine for treating their refractory pain (Koulmann et al., 2004), animal studies (Alvarez et al., 2003; Castel et al., 2013), experimental studies in humans (Graven-Nielsen et al., 2000) and several RCTs (Mercadante et al., 2000) have demonstrated the beneficial effect of ketamine in chronic pain. Besides lowering pain, ketamine helped with mood, physical activity and quality of life. The number of patients is rather small because we treated only refractory pain syndromes with ketamine, but is larger than most studies reporting results of ketamine use for chronic pain. Our use of three treating protocols over time may be a weakness, but highlights the good tolerability of oral ketamine when dose titration is particularly careful. Finally, a total of 51% of our patients were not receiving opioids during ketamine administration, but most of these patients had previously shown failure or diminishing efficacy of opioid therapy.

6. Conclusions

Despite the uncertainty alleged by previous reviews and meta-analyses, our retrospective study of 51 patients found that when chronic pain becomes intractable despite conventional treatment, ketamine might be a useful alternative. In nearly two-thirds of patients, ketamine reduced chronic pain temporarily or in the long term. Our main result is that the longer patients receive an opioid treatment, the more ketamine should be an option, with more likely analgesic efficacy and less likely secondary effects. Moreover, we confirm that ketamine may be useful for opioid withdrawal. Although some patients may hope for prolonged treatment with ketamine, the treatment duration should be as limited as possible because of its potentially harmful secondary effects.

Author contributions

F.M. gathered the patients, collected the data and participated in the redaction of the paper. A.C. gathered the patients and participated in the redaction of the paper. A.B. and C.M. realized all the work on ketamine oral solution. P.B. participated in the redaction of the paper. G.M. discussed the study protocol, collected the data, made the statistical comparisons and wrote the paper. The authors are indebted to Amy Usner for her kind reviewing of the paper.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Median oral ketamine dose (dot; whiskers: interquartile range 25–75%) for 55 cases.
Figure S2. Median duration of oral ketamine treatment (dot; whiskers: interquartile range 25–75%). Extreme value corresponds to a 22-year-old patient with a genetic disease who received oral ketamine in a compassionate protocol.
Table S1. Characteristics of treatment by ketamine: treatment response.
Table S2. Effect of pain lowering with ketamine on working function**.**
Table S3. Characteristics of patients with and without adverse effects with ketamine treatment.