

# Dextromethorphan and memantine after ketamine analgesia: a randomized control trial

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**Purpose:** Intravenous ketamine is often prescribed in severe neuropathic pain. Oral *N*-methyl-D-aspartate receptor (NMDAR) antagonists might prolong pain relief, reducing the frequency of ketamine infusions and hospital admissions. This clinical trial aimed at assessing whether oral dextromethorphan or memantine might prolong pain relief after intravenous ketamine.

**Patients and methods:** A multicenter randomized controlled clinical trial included 60 patients after ketamine infusion for refractory neuropathic pain. Dextromethorphan (90 mg/day), memantine (20 mg/day) or placebo was given for 12 weeks (n=20 each) after ketamine infusion. The primary endpoint was pain intensity at one month. Secondary endpoints included pain, sleep, anxiety, depression, cognitive function and quality of life evaluations up to 12 weeks.

**Results:** At 1 month, dextromethorphan maintained ketamine pain relief (Numeric Pain Scale: 4.01±1.87 to 4.05±2.61,  $p=0.53$ ) and diminished pain paroxysms ( $p=0.03$ ) while pain intensity increased significantly with memantine and placebo ( $p=0.04$ ). At 3 months, pain remained lower than at inclusion ( $p=0.001$ ) and was not significantly different in the three groups. Significant benefits were observed on cognitive-affective domains and quality of life for dextromethorphan and memantine ( $p<0.05$ ).

**Conclusions:** Oral dextromethorphan given after ketamine infusion extends pain relief during one month and could help patients to better cope with pain. Future studies should include larger populations stratified on pharmacogenetics screening. Optimization of an oral drug that could extend ketamine antihyperalgesia, with fewer hospital admissions, remains a prime challenge in refractory neuropathic pain.

**Keywords:** *N*-methyl-D-aspartate antagonists, peripheral neuropathic pain, drug relay, cognitive-affective status, health-related quality of life

## Introduction

Chronic pain with neuropathic characteristics has a prevalence of 7–10% in the general population.<sup>1</sup> Failure of neuropathic pain (NP) treatment with recommended drugs is common in clinical practice,<sup>2</sup> and antagonists of the *N*-methyl-D-aspartate receptor (NMDAR), a receptor known to play an important role in the development of central pain sensitization,<sup>3</sup> have been studied with contradictory results.<sup>4–8</sup> Ketamine has been shown to be effective for the treatment of postoperative pain,<sup>9</sup> post-herpetic neuralgia<sup>6</sup> and phantom-limb pain,<sup>10</sup> but displayed no analgesic effect in other studies like surgery-induced NP.<sup>11,12</sup> Ketamine is widely used in pain clinics to treat NP and is reported to be effective in 30–65% patients.<sup>13–15</sup> Pain alleviation diminishes however after a few weeks or months,<sup>16,17</sup> requiring hospital

readmission for another intravenous ketamine infusion. Furthermore, because of its psychodysleptic, cardiovascular and hepatic side-effects, its use should be limited to short-term administration.<sup>18</sup>

Other NMDAR antagonists are available in oral form. Dextromethorphan, a cough suppressant and memantine, prescribed in Alzheimer's disease to maintain cognitive function, have minimal side-effects compared to ketamine at therapeutic doses. Memantine for NP alleviation was preventive in human studies,<sup>7,19</sup> but ineffective in the treatment of postherpetic neuralgia.<sup>20</sup> Dextromethorphan alleviates NP in diabetes<sup>21,22</sup> and trauma<sup>4,5</sup> but has no beneficial effect on NP in other clinical trials.<sup>8,23</sup> Genetic polymorphism has been identified as a variability factor of dextromethorphan (*CYP2D6*, *CYP3A4* and *ABCB1*) and memantine (*NR1I2*) metabolism, and may be involved in the modulation of their analgesic effect.<sup>4,5,24</sup>

With the aim of limiting ketamine infusions (whose long term repeated effects are poorly known) and hospital admissions, we hypothesized that oral NMDAR antagonists could be a therapeutic option in patients relieved by ketamine. The objectives of the present trial were to assess whether one to three months treatment with oral dextromethorphan or memantine, that have similar chemical structures and target receptors than ketamine but with fewer side effects, could be effective relays of ketamine for the management of refractory neuropathic pain and of its cognitive-affective impact.

## Materials and methods

### Study design

This randomized, controlled, single-blind (patients blinded) trial was conducted in seven French Pain Clinics with 60 patients suffering from severe NP. The study was coordinated by the Clinical Research Center, University Hospital of Clermont-Ferrand, France and has been approved by the regional Ethics committee, CPP Sud-Est VI (leading ethics committee number AU 895) and registered at "http://www.clinicaltrials.gov" (NCT01602185). Recruitment started in March 2012 and the last visit of the last patient was in July 2016. This manuscript adheres to the applicable CONSORT guidelines. Patients provided written informed consent prior to their participation in the study.

The present study aimed to assess analgesia by dextromethorphan and memantine in patients who have infusions of ketamine for refractory neuropathic pain. Ketamine was administered in ampoules of 50 mg/5 mL intravenously

with an electric syringe at the dose of 0.4–0.5 mg/kg diluted in 45 mL of physiological saline (0.9% NaCl) for 2 hrs according to the usual procedures of the pain clinic. After their ketamine infusion, patients were randomly assigned to oral dextromethorphan (n=20), memantine (n=20) or placebo (n=20) for twelve weeks. A person not involved in the study generated the randomization sequence using random blocks with Stata Software (Version 13, StataCorp, College Station, TX). Dextromethorphan (Pulmodexane<sup>®</sup> 30 mg, Bailly-Creat Laboratory) and memantine (Ebixa<sup>®</sup> 10 mg and 20 mg, Lundbeck SAS) were given in increasing doses: dextromethorphan: 30 mg/day (week 1); 60 mg/day (week 2); 90 mg/day (weeks 3 to 12); memantine: 5 mg/day (week 1); 10 mg/day (week 2); 15 mg/day (week 3); 20 mg/day (weeks 4 to 12). Placebo (lactose tablet) was given once a day for twelve weeks. Treatments were prepared and conditioned in the Central Hospital Pharmacy by a qualified pharmacist according to good manufacturing principles. Treatment compliance was assessed at the end of the trial by two persons independent of the protocol.

Questionnaires and cognitive tests were carried out at the inclusion visit (pre ketamine infusion: preK or inclusion), 3 days after ketamine infusion (postK), at Month 1 (M1), Month 2 (M2) and Month 3 (M3). In order to maintain good compliance and safety, patients were contacted once a week by phone. A paper pain diary completed by patients included concomitant analgesic treatments, and adverse events. A blood sample was collected at the end of the trial to study the polymorphism of genes involved in the metabolism and bioavailability of dextromethorphan (*CYP2D6*, *CYP3A4* and *ABCB1*) and in the excretion of memantine (*NR1I2*).

### Participants and setting

All patients fulfilled the following inclusion criteria:  $\geq 18$  years of age, suffering from peripheral NP excluding central or diabetic origin and relieved by ketamine (defined as a decrease of 1.5 point on the NPS three days following the ketamine infusion). They had to be registered to the French Health care system and have given written informed consent.

Exclusion criteria included contraindication to dextromethorphan or memantine (hypersensitivity to the active substance or the excipients, hypertension, history of stroke, severe heart failure or diabetes Type I and II), medical and/or surgical history not compatible with the study, progressive disease at the inclusion visit, alcohol

addiction and treatment with specific drugs (ketamine, dextromethorphan, memantine, amantadine, L-Dopa, dopaminergic agonists, anticholinergic, barbituric, neuroleptic, IMAO, antispastic agents, dantrolen or baclofen, phenytoin, cimetidine, ranitidine, procainamide, quinidine, quinine, nicotine, hydrochlorothiazide, warfarine). Women of childbearing potential not using an effective contraceptive, pregnant or breastfeeding were also excluded.

## Primary and secondary endpoints

The primary endpoint was the pain intensity evaluation at M1 by NPS in the past 24 hrs in the 3 groups. The primary outcome was the comparison of pain intensity between M1 and postK. Secondary endpoints included pain assessment: NPS, Brief Pain Inventory (BPI), McGill pain questionnaire, Neuropathic Pain Symptom Inventory (NPSI), quality of life: Short-Form 36 (SF-36), Leeds Sleep Evaluation Questionnaire (LSEQ), anxiety and depression: Hospital Anxiety Depression Scale (HADS), cognition: Cantab<sup>®</sup> Tests and concomitant analgesic treatments (paper pain diary), at preK, postK, M1, M2 and M3.

Details concerning the different scales and questionnaires used in the present study (NPS, DN4 (Douleur Neuropathique en 4 questions), NPSI, BPI, McGill Pain Questionnaire, HADS, LSEQ, SF-36 and Cantab<sup>®</sup> Tests) are available in the rationale and design article previously published.<sup>25</sup> Following information concerns only the Cantab<sup>®</sup> outcome measures.

### Reaction time (RTI)

The outcome measure is the five-choice reaction time latency, measured in milliseconds, *ie* the speed with which the patient releases the press pad button in response to the visual stimulus.

### Information sampling task (IST)

The outcome measure chosen is the number of sampling errors in decreasing win condition, *ie* the number of trials in which the subject chose a colour that was not in the overall majority but was in the majority at the point of decision.

### Stockings of cambridge (SOC)

The chosen outcome is the number of problems solved in minimum moves.

### Graded naming test (GNT)

Results are expressed as the percentage of correct answers.

## Pharmacogenetic analyses

Genotyping was performed from blood extract of 13 patients in dextromethorphan group (*CYP2D6*, *CYP3A4*, and *ABCB1*) and 13 patients in memantine group (*NR1I2*). Genomic deoxyribonucleic acid (DNA) was extracted from blood mononuclear cells by use of a commercial kit (Maxwell<sup>®</sup> 16 LEV Blood DNA Kit Promega, Charbonnières-les-Bains, France) according to the manufacturer's protocols.

***CYP2D6* genotyping** The *CYP2D6\*6* allele was detected by use of the long Polymerase Chain Reaction (PCR) method for the whole-gene amplification, followed by a subsequent nested PCR and restriction enzyme analysis.<sup>26</sup> Gene deletion (*CYP2D6\*5* allele) and gene duplication (responsible for ultrarapid phenotype) were analyzed by the long PCR method as previously described.<sup>27</sup> *CYP2D6\*3* and *CYP2D6\*4* were detected by use of Taq Man<sup>®</sup> Drug Metabolism Genotyping Assays (Applied Biosystems-Thermo Fischer Scientific, Courtaboeuf, France).

***CYP3A4* genotyping** *CYP3A4\*1B*, *CYP3A4\*22* and *CYP3A5\*3* were detected by Taq Man<sup>®</sup> Drug Metabolism Genotyping Assays.

***ABCB1* genotyping** In the literature *C3435T* and *G2677T/A* are the most widely investigated SNPs of the *ABCB1* gene and were identified by Taq Man<sup>®</sup> Drug Metabolism Genotyping Assays. The polymorphic allele 3435T is associated with decreased P glycoprotein (P-gp) expression in placenta, liver and leukocytes but controversial results were reported on the association of the allele 2677T/A and a diminished P-gp expression.<sup>28</sup>

***NR1I2* genotyping** In the literature the *NR1I2* rs1523130 SNP was found to be significantly associated with memantine clearance with carriers of the *NR1I2* rs1523130 CT/TT genotypes presenting 16% slower memantine excretion than the CC genotype carriers.<sup>24</sup> Genotyping was performed by Taq Man<sup>®</sup> Drug Metabolism Genotyping Assays.

## Statistical analysis

According to previous publications,<sup>8</sup> it seemed reasonable to consider that the standard deviation of the primary outcome was ranged between 1.2 and 1.5 points. According to these assumption, 20 patients per group allow to detect a true a minimal difference greater than 1.4 points on the primary outcome (for a standard-deviation equals 1.35 and an effect-size around 1), a type I error at 0.017 (inflate to take into account multiple comparisons) and a statistical power at 80%.

Statistical analyses were performed using Stata software (Version 13, StataCorp, College Station, US) and

were conducted for a two-sided Type I error of 5%. Continuous data were presented as mean  $\pm$  standard-deviation or median [interquartile range] according to statistical distribution, and categorical parameters as the number of patients and associated percentages. Comparisons have considered usual statistical tests: ANOVA or Kruskal-Wallis tests if conditions of ANOVA were not met for quantitative variables (NPS, DN4, NPSI, BPI, McGill Pain Questionnaire, HADS, LSEQ, SF-36 and Cantab<sup>®</sup> Tests). The normality was studied using Shapiro-Wilk test and the homoscedasticity was analyzed using Bartlett test. When appropriate (omnibus  $p$ -value $<0.05$ ), a post-hoc test has been performed to take into account multiple comparisons: Tukey-Kramer post ANOVA and Dunn after Kruskal-Wallis. More precisely, the primary analysis was intent-to-treat and has been performed according to Vickers and Altman recommendations considering an analysis of covariance with baseline values as covariate. Finally, concerning the analysis of repeated measures, random-effect models were carried out to study fixed effects (group, time-points and interaction group  $\times$  time), taking into account between and within subject variability (patient as random-effect). A Sidak's correction has been applied to take into account multiple comparisons between groups. The normality of residuals was checked for each model. When appropriate, a log transformation was proposed to achieve the normality of endpoints considered as dependent variables in these models. The assessment of ketamine analgesic effect has been evaluated using paired tests: Student  $t$ -test or Wilcoxon if appropriate. Most analyses of secondary outcome parameters seem exploratory. So, as proposed by several statisticians, we chose to report the individual  $p$ -values associated to secondary endpoints without doing any mathematical correction for distinct tests comparing groups.<sup>29</sup> A particular focus was given to the magnitude of differences and to the clinical relevance.<sup>30</sup>

## Results

### Study subjects

In this study, 132 patients were pre-screened, 24 patients refused to participate, 43 did not meet the inclusion criteria and 65 gave written informed consent. Out of these, 60 were randomized and analyzed for primary endpoint at M1 ( $n=20$  in each treatment group), 52 completed the study up to M2 (D: 18; M: 18; PI: 16) and 47 completed the entire study up to M3 (D: 17; M: 16; PI: 14). Figure 1 shows the

CONSORT flow diagram. Eligible patients were recruited from May 2012 to January 2016 and the study finished in July 2016. Table 1 shows the baseline characteristics of the participants. At baseline, NP was confirmed by a DN4 $\geq 4/10$  (D: 6.3 $\pm$ 1.9; M: 5.9 $\pm$ 1.7; PI: 6.2 $\pm$ 1.0). Medical practitioners were not required to modify their usual ketamine administration (continuous intravenous 0.4 to 0.5 mg/kg/2 hrs via electric syringe pump).

### Primary outcome

At M1, intragroup comparisons of NPS scores between postK and M1 indicated that pain intensity did not increase with dextromethorphan (4.01 $\pm$ 0.25 to 4.05 $\pm$ 0.58,  $p=0.53$ ) while pain intensity increased significantly with memantine and placebo (M: 4.01 $\pm$ 0.25 to 5.88 $\pm$ 0.52,  $p=0.04$ ; P: 4.01 $\pm$ 0.25 to 4.98 $\pm$ 0.50,  $p=0.04$ ) (Figure 2).

### Secondary outcomes

#### Pain outcomes

At M1, the pain intensity of the 60 patients in the three randomized groups tended to be lower for dextromethorphan (D: 4.05 $\pm$ 0.58; M: 5.88 $\pm$ 0.52; PI: 4.98 $\pm$ 0.50;  $F_{(2,57)}=2.9$ ,  $p=0.06$ ) (Figure 2).

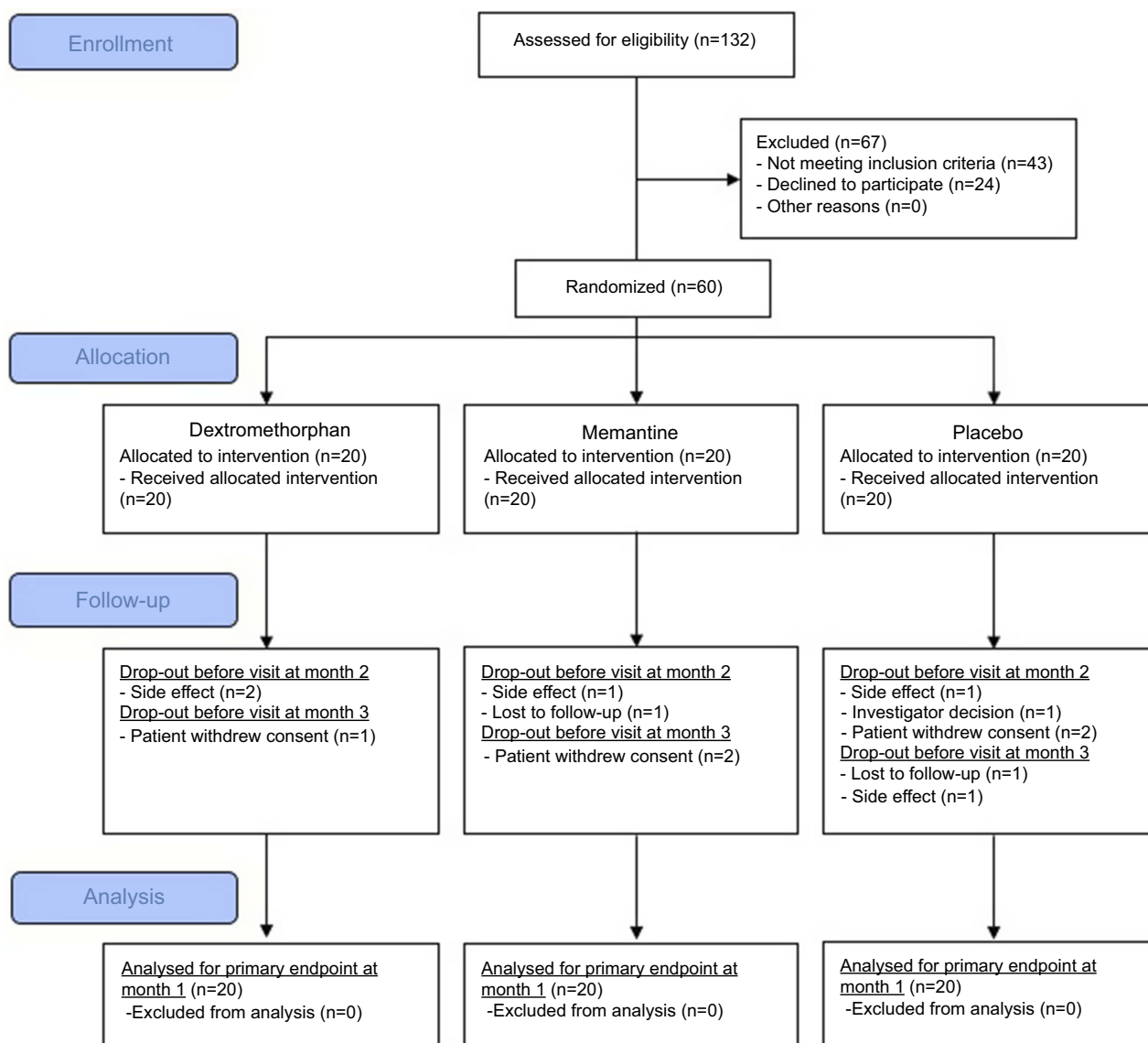
At M3, dextromethorphan, memantine and placebo were not significantly different ( $p=0.51$ ) (Figure 2); dextromethorphan and memantine were not significantly different from placebo and pain that remained lower than at inclusion ( $p=0.001$ ).

At M1, concerning BPI, "worst pain" intensity and "walking inability" were significantly lower in the dextromethorphan group compared with memantine and placebo groups ("worst pain": D: 4.75 $\pm$ 2.75; M: 6.95 $\pm$ 2.37; PI: 6.15 $\pm$ 2.54;  $p=0.03$ ; "walking inability": D: 4.00 $\pm$ 3.45; M: 6.25 $\pm$ 2.94; PI: 4.35 $\pm$ 3.50;  $p=0.049$ ) (Figure 4A).

No significant difference was observed in the other BPI items or in the other pain questionnaires (NPSI, McGill Pain Questionnaire).

#### Cognitive-affective outcomes

Cognitive tests (CANTAB<sup>®</sup>) were performed in 20 patients (D,  $n=7$ ; M,  $n=7$ ; P,  $n=6$ ) in one pain clinic for practical reasons. With dextromethorphan, between postK and M3, IST test accuracy was improved specifically in the decreasing win condition, with a negative score difference (delta) of sampling errors (D: -0.86 $\pm$ 0.69; M: 0.40 $\pm$ 0.55; PI: 0.00 $\pm$ 0.00;  $p=0.02$ ) (Figure 3B). Between postK and M1, M2, M3, no significant difference was shown for RTI and GNT parameters. With memantine, between



**Figure 1** Flowchart of participants during the trial.

postK and M1, more memory problems (SOC test) were solved in minimum moves than in the placebo group (scores differences (delta) (D:  $1.14 \pm 1.57$ ; M:  $2.20 \pm 1.92$ ; PI:  $-0.80 \pm 1.48$ ;  $p=0.04$ ) (Figure 3A). At postK there was no statistical difference between the three groups for the RTI, GNT, IST and SOC tests.

Scores of anxiety and depression (HADS) at M1, M2 and M3 were not significantly different between the three groups. Between postK and M1, M2, M3, no significant difference was shown for anxiety and depression scores in the three groups. However, at M2, significantly more safe cases of anxiety ( $\geq 11$ ) were observed in the placebo group compared to the dextromethorphan and memantine groups ( $p=0.003$ ).

### Quality of life outcomes

At M2, higher scores in dextromethorphan and memantine were observed concerning the quality of life parameters assessed (SF-36) and a significant difference was observed in the “general health” sub-score (D:  $50.06 \pm 19.08$ ; M:  $53.06 \pm 23.08$ ; PI:  $34.06 \pm 20.23$ ;  $p=0.03$ ) (Figure 4B).

At M3 a significant difference was shown in “vitality” sub-score with a higher score in memantine group (D:  $32.35 \pm 18.88$ ; M:  $48.44 \pm 14.80$ ; PI:  $37.14 \pm 14.64$ ;  $p=0.02$ ) (Figure 4B).

Between postK and M3, the percentage change of “role emotional” sub-score was more important in the memantine group than in the dextromethorphan and placebo

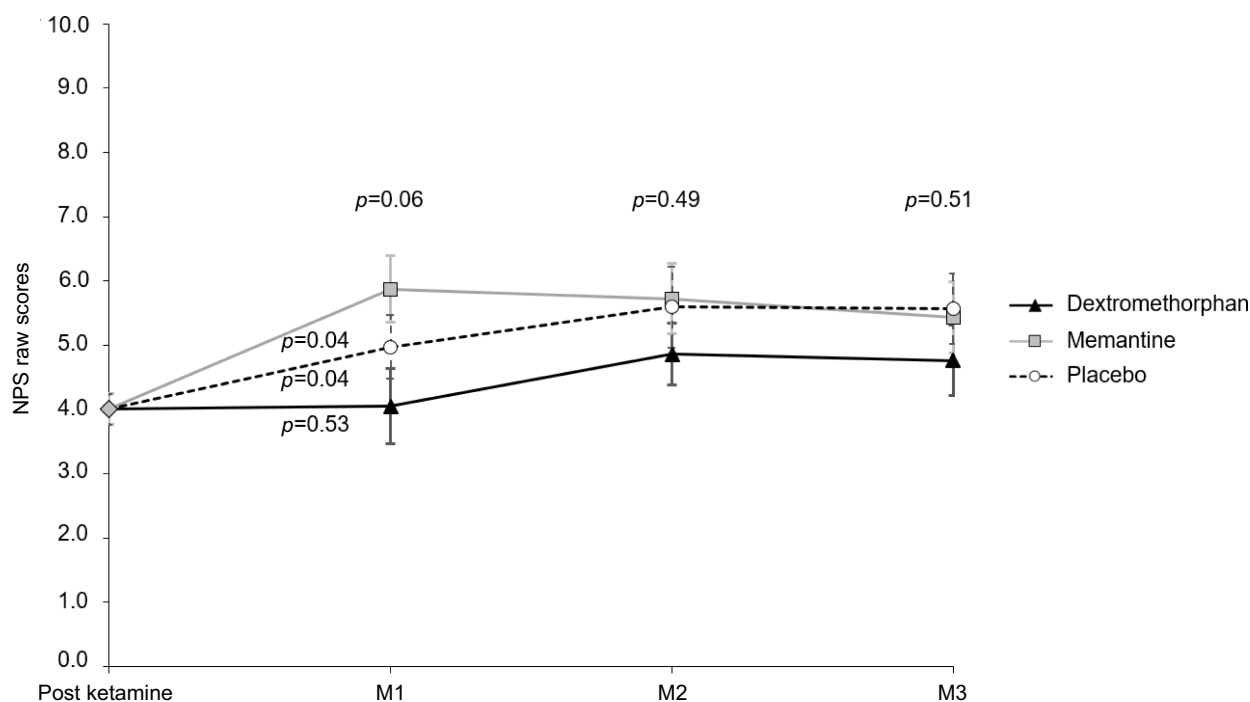


**Table 1** Demographics and clinical baseline (preK) characteristics

	General population n=60	Dextromethorphan n=20	Memantine n=20	Placebo n=20
<b>Age (mean [min, max])</b>	51.6 [32, 77]	50.6 [34, 72]	51.7 [37, 77]	52.6 [32, 73]
<b>Gender, n (%) Female</b>	37 (61.7)	16 (80.0)	9 (45.0)	12 (60.0)
Male	23 (38.3)	4 (20.0)	11 (55.0)	8 (40.0)
<b>Pain diagnoses, Post-trauma n (%) Post-surgery</b>	34 (56.8)	12 (60.0)	11 (55.0)	11 (55.0)
Post-chemotherapy	18 (30.0)	4 (20.0)	6 (30.0)	8 (40.0)
Phantom-limb pain	2 (3.3)	0 (0.0)	2 (10.0)	0 (0.0)
Fibromyalgia	2 (3.3)	2 (10.0)	0 (0.0)	0 (0.0)
Alcoholic neuropathy	2 (3.3)	0 (0.0)	1 (5.0)	1 (5.0)
<b>NPS score (mean ± S.D.)</b>	6.89±1.88	6.40±1.85	7.20±2.26	7.08±1.47
<b>DN4 score (mean ± S.D.)</b>	6.12±1.59	6.30±1.87	5.85±1.73	6.20±0.95
<b>NPSI total score (mean ± S.D.)</b>	47.76±14.18	46.20±14.86	46.20±12.97	50.88±14.83

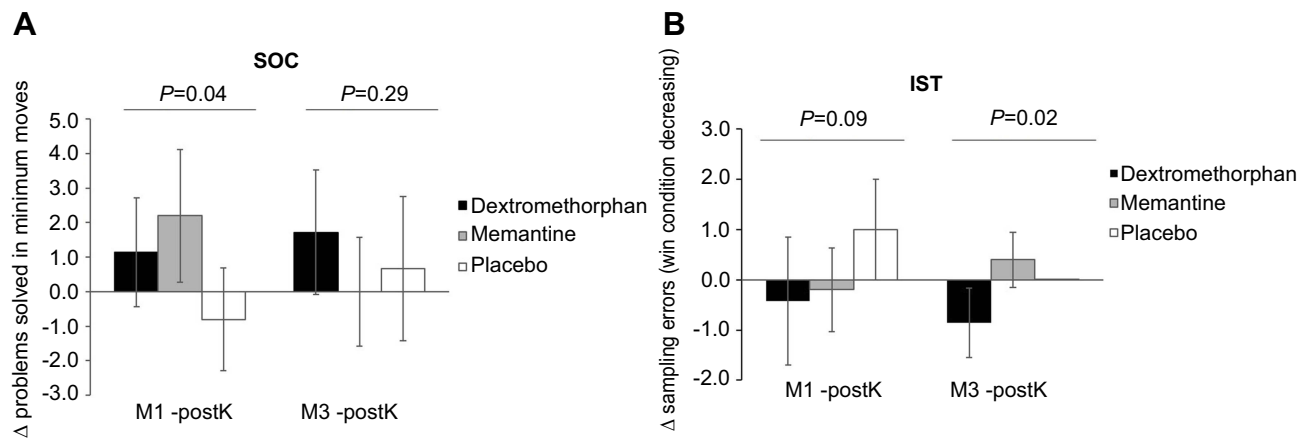
**Notes:** No statistical significant difference between groups in any sociodemographic or clinical variable was observed, indicating that groups were comparable for the variables measured.

**Abbreviations:** DN4, Douleur Neuropathique en 4 questions; NPS, Numeric Pain Scale; NPSI, Neuropathic Pain Symptom Inventory; PreK, pre ketamine infusion; S.D., Standard Deviation.

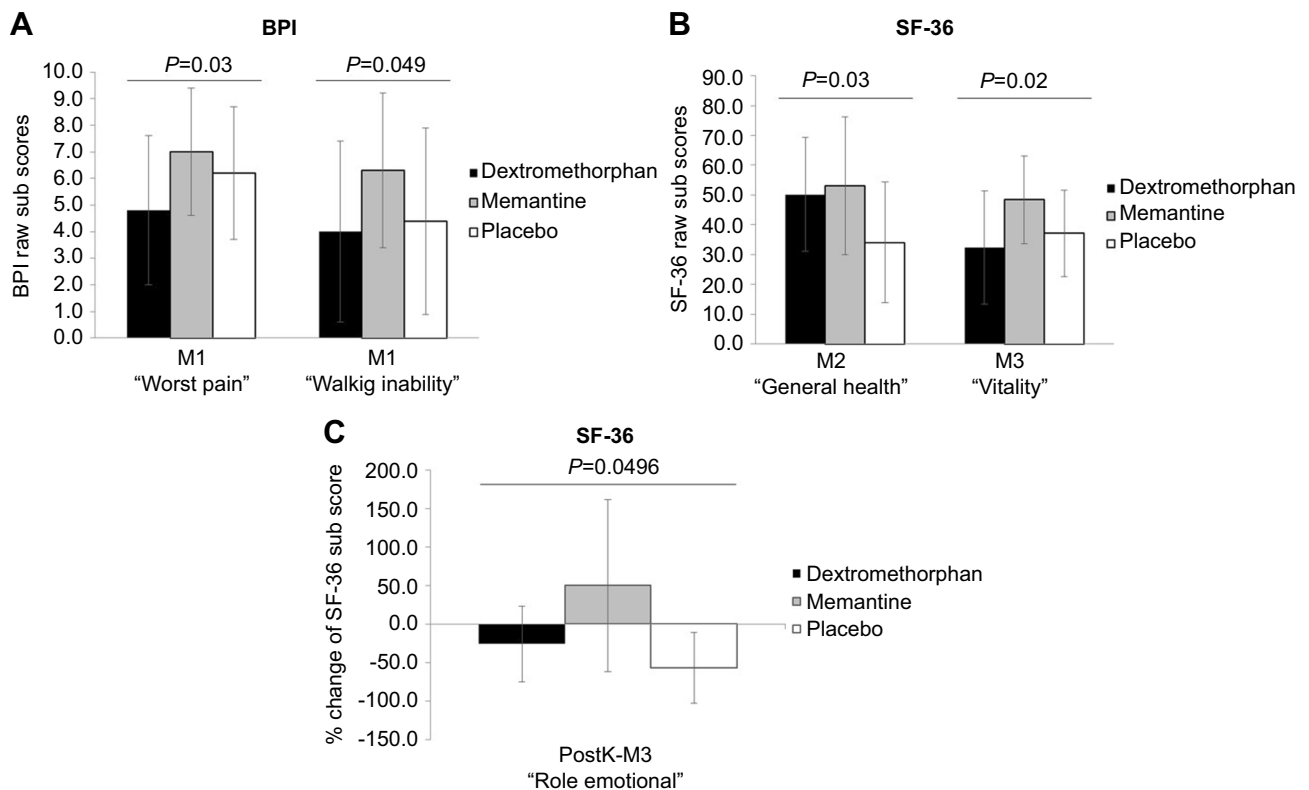


**Figure 2** Effect of dextromethorphan, memantine and placebo on pain intensity assessed by Numeric Pain Scale (NPS, mean ± SEM) after ketamine infusion in patients with neuropathic pain at Month 1, 2 and 3 (M1, M2, M3).

**Notes:** Intragroup comparisons between post ketamine and M1 indicate that pain intensity does not increase with dextromethorphan ( $p=0.53$ ) while pain intensity increases significantly with memantine and placebo ( $p=0.04$ ). Pain intensity tends to be lower for dextromethorphan ( $p=0.06$  at M1).



**Figure 3** Effect of dextromethorphan, memantine and placebo on cognitive parameters assessed with the CANTAB<sup>®</sup> between postK and M1 (**A**), and postK and M3 (**B**). **Notes:** Delta ( $\Delta$ ) represents the cognitive score difference between M1 or M3 and postK. (**A**) At M1, significant differences were observed between the three groups in the SOC test ( $p=0.04$ ) and (**B**) at M3 in the IST test ( $p=0.02$ ). **Abbreviations:** IST, Information Sampling Task; M1, Month 1; M3, Month 3; postK, post ketamine infusion; SOC, Stockings of Cambridge.



**Figure 4** Effect of dextromethorphan, memantine and placebo on Brief Pain Inventory (BPI) score and Short-Form 36 (SF-36) parameters assessed after ketamine infusion (postK), Month 1, 2 and 3 (M1, M2, M3). **Notes:** (**A**) Scores of "Worst pain" and "Walking inability" BPI sub-scores assessed at M1 were significantly decreased in the dextromethorphan group compared to memantine and placebo groups. (**B**) Scores of "General health" and "Vitality" SF-36 sub scores were significantly higher in the memantine group at M2 and M3 respectively compared to dextromethorphan and placebo groups. (**C**) Percentage change (%) represents the difference between postK and M3 of "Role emotional" SF-36 sub score. At M3 "Role emotional" sub score increases significantly in memantine group compared to dextromethorphan and placebo groups.

groups (D:  $-25.75 \pm 49.08$ ; M:  $46.97 \pm 111.51$ ; Pl:  $-57.14 \pm 46.00$ ;  $p=0.0496$ ) (Figure 4C).

No significant difference was observed in the other SF-36 sub-scores or in the LSEQ.

### Ketamine antihyperalgesic effect

Pain intensity decreased significantly (Table S1) between inclusion and postK ( $6.89 \pm 1.88$  to  $4.01 \pm 1.87$ ,  $p < 0.0001$ ) and was maintained throughout the 3 months follow-up (Figure 2). NP characteristics assessed by the NPSI questionnaire and the BPI sub-scores also decreased significantly after ketamine infusion ( $p < 0.0001$ ). Anxiety and depression scores assessed by HADS were significantly reduced (HADS anxiety:  $p=0.007$ ; HADS depression:  $p=0.04$ ). The percentage of safe cases ( $\geq 11$ ) decreased significantly on the anxiety subscale ( $p=0.0497$ ) but not on depression subscale ( $p=0.39$ ). Sensory and affective dimensions of pain assessed by the McGill pain questionnaire were also significantly diminished ( $p < 0.0001$  and  $p=0.001$  respectively). Sleep efficiency sub-scores of LSEQ were increased with ketamine (quality of sleep:  $p=0.0001$ ; ease of waking:  $p=0.04$ ; behavior following wakefulness:  $p < 0.0001$ ; ease of initiating sleep; ( $p=0.05$ ) (Table S1)).

### Pharmacogenetics results

Baseline characteristics on *CYP2D6*, *CYP3A4*, *ABCB1* and *NR1I2* genotype and phenotype distributions of 26 patients are provided in Table S2. In the dextromethorphan group, it was noticed concerning *ABCB1 C3435T* genotype that all the homozygous *3435TT* patients presented a decrease of pain intensity between postK and M1 (a mean decrease of  $-1.67$  on the NPS score) contrary to *3435CT* (33.3%) (a mean decrease of  $-1.83$  on the NPS score) and *3435CC* (0.0%) patients ( $p=0.08$ ). Between postK and M1, M2 or M3, no significant results were observed concerning the impact of the different genotypes on the analgesic efficacy of dextromethorphan and memantine.

### Adverse events

The proportion of patients experiencing various non-serious adverse events in the dextromethorphan, memantine and placebo groups was: 45.0%, 30.0% and 25.0%, respectively ( $p=0.38$ ), and only 8 patients experienced possibly drug-related non-serious adverse events (D: 25.0%; M: 15.0%,  $p=0.73$ ) such as drowsiness and nausea in dextromethorphan group, and dizziness, drowsiness and constipation in memantine group.

## Discussion

The present study explored in patients with chronic refractory pain if the pain relief provided by intravenous ketamine could be maintained by oral NMDAR antagonists, dextromethorphan and memantine. After one month treatment, oral dextromethorphan maintained ketamine antihyperalgesia and reduced significantly paroxysmal pain ( $p=0.03$ ), a type of pain that patients have substantial difficulty to cope with, as pain paroxysms may be very severe and unpredictable. Genetic polymorphism has been identified as a variability factor of dextromethorphan<sup>4,5,24</sup> and pharmacogenetics screening suggests that the dextromethorphan responders were *ABCB1 3435TT*, a profile reported in the literature to display lower P-gp expression than *ABCB1 3435CC* and *3435CT* patients,<sup>28,31</sup> and to be associated with increased dextromethorphan bioavailability, increased blood-brain barrier crossing and enhanced analgesic effect.

After 3 months treatment, some relief was still present in the three groups, as pain score did not reach the initial intensity reported before ketamine infusion ( $p < 0.001$ ). However, the blunting of the strong antihyperalgesic effect of dextromethorphan after the first month may be linked to the low dosage (90 mg/day), as clinical success in NP treatment has been reported with higher doses up to 960 mg/day,<sup>4,8</sup> at the expense of adverse events. Moreover, it has been shown that dextromethorphan requires increasing dosages to maintain analgesic efficacy over time,<sup>32,33</sup> explaining the attenuation of the momentum in dextromethorphan analgesic effect.

Other beneficial effects were observed in this study. Dextromethorphan improved decision-making, overcoming the decision-making deficits frequently reported in chronic pain patients.<sup>34</sup> Memantine and dextromethorphan both improved general health ( $p=0.03$ ) and several domains of cognition including cognitive test accuracy ( $p=0.02$ ). Memantine improved vitality, spatial planning, thinking, and problem solving. It also improved affective aspects of pain ("role emotional" sub-score of the SF-36) at three months, suggesting that patients were feeling better despite the presence of pain, and that the impact of impaired emotional health on social activities was less salient in this group. This affective impact is explained by the high rate of NMDAR in the hippocampus, a pivotal area of memantine action on cognitive and memory processes, and in the anterior cingulate cortex and forebrain, with probable impact on the affective quality of pain and sensory-limbic



dissociation in pain experience.<sup>7</sup> Dextromethorphan and memantine also confirmed their suggested beneficial effect on anxiety at two months, but not on depression.<sup>35</sup>

Ketamine, recently approved by the FDA as a nasal spray antidepressant, on its own displayed a long-term antihyperalgesic effect as already reported in chronic pain patients,<sup>36</sup> where ketamine onset/offset half-life exceeds the acute pain relief time.<sup>16,17</sup> A half-life of 11 days was estimated in patients with Complex Regional Pain Syndrome treated with 20–30 mg/hr of S-ketamine during 100 hrs, indicating a persistent ketamine effect dissipating after about 55 days,<sup>16,17,36</sup> but the extended antihyperalgesic effect of ketamine is not elucidated. The analgesic potency of metabolites (dehydronorketamine, norketamine and hydroxynorketamine) and their interaction with NMDAR are not well known.<sup>37–39</sup> Ketamine is metabolized via cytochrome P450 and interactions are possible, considering that patients maintained their usual treatment with an average of 4.6 medications that could have interfered with metabolite synthesis. Finally, the long-lasting antihyperalgesic effect of ketamine may be explained by prolonged or persistent blockade of MAP kinases, PKC- $\gamma$  and ERK signaling pathways, permanently remodeling pain processing in the nervous system even after the total excretion of ketamine.<sup>9</sup>

Ketamine also induced short-term analgesia ( $p < 0.0001$ ), related to its ability to rapidly pass the blood–brain barrier, ensuring quick onset of acute analgesia.<sup>40,41</sup> It also had antidepressant ( $p = 0.04$ ) and anxiolytic ( $p = 0.007$ ) effects that might be linked to an increase in brain-derived neurotrophic factor concentration in the hippocampus.<sup>42</sup> Improvement in pain and emotional status was accompanied by better daily function ( $p = 0.009$ ) and sleep ( $p = 0.0001$ ). These results are particularly important in chronic pain patients who often have depressive disorders<sup>43</sup> and impaired health-related quality of life,<sup>44</sup> these aspects being explored in a large ongoing observational trial in chronic refractory pain patients (NCT03319238).

## Conclusion

Oral dextromethorphan temporarily extended ketamine pain relief over one month and future studies should include larger populations and pharmacogenetics screening. Cognitive-affective dimensions were improved with dextromethorphan and memantine, suggesting these drugs could help patients to establish pain-coping strategies. Knowledge on long-term repeated use of intravenous ketamine in chronic pain is poorly known and the opportunity of an analgesic oral drug that could

extend ketamine analgesia with fewer hospital admissions remains a prime challenge.

## Availability of data and materials

All available data are in the manuscript and no other document will be made available.

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## Author contributions

Conceived and designed the experiments: GP, MS, FM, FT, PP, ND, M-CC, MN, RC, CC, BL, GBM, AMD. Performed the experiments: GP, EM, VM, MS, FM, FT, PP, ND, M-CC, MN, RC, CC, BL, GBM, AMD. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary materials

**Table S1** Effect of ketamine on the Numeric Pain Scale (NPS), Neuropathic Pain Symptom Inventory (NPSI), Brief Pain Inventory (BPI), McGill Pain questionnaire, Hospital Anxiety and Depression Scale (HADS) and Leeds Sleep Evaluation Questionnaire (LSEQ) between preK and postK

	preK n=60	postK n=60	p-value
NPS	6.89±1.88	4.01±1.87	< 0.0001
NPSI total score	47.76±14.18	36.05±18.10	< 0.0001
BPI patient pain experience	5.85±1.49	4.52±1.79	< 0.0001
BPI pain severity	6.16±1.64	4.41±1.93	< 0.0001
BPI REM	4.56±2.68	3.16±2.69	< 0.001
BPI WAW	6.49±1.90	5.70±2.29	< 0.01
HADS anxiety (mean ± S.D.)	9.22±4.45	7.98±4.07	< 0.01
HADS depression (mean ± S.D.)	8.37±4.15	7.45±3.82	0.04
McGill Pain sensorial score	49.66±23.39	36.80±21.43	< 0.0001
McGill Pain affective score	43.37±19.14	33.60±18.65	0.001
LSEQ ease of initiating sleep	-2.98±9.34	-0.10±8.60	0.05
LSEQ quality of sleep	-4.85±4.52	-1.13±6.17	0.0001
LSEQ ease of waking	-0.31±8.43	2.18±8.14	0.04
LSEQ behavior following wakefulness	-1.62±5.45	1.52±5.30	0.0001

**Notes:** Statistical significant differences were observed between preK and postK in the 60 patients in NPS, NPSI, BPI, McGill Pain questionnaire, HADS and LSEQ questionnaires. No significant difference was observed in LSEQ ease of initiating sleep sub score.

**Abbreviations:** BPI, Brief Pain Inventory; BPI REM, Affective interference; BPI WAW, Activity interference; HADS, Hospital Anxiety Depression Scale; LSEQ, Leeds Sleep Evaluation Questionnaire; NPS, Numeric Pain Scale; NPSI, Neuropathic Pain Symptom Inventory; postK, post ketamine infusion; preK, pre ketamine infusion; S.D., Standard Deviation.

**Table S2** Pharmacogenetic characteristics of patients in the dextromethorphan and memantine groups

Dextromethorphan n=13				Memantine n=13	
CYP2D6 genotypes	n (%)	ABCB1 C3435T genotypes	n (%)	NR1I2 rs1523130 genotypes	n (%)
*1/*xN	0 (0.0)	CT	9 (69.2)	CC	8 (61.5)
*1/*1	7 (53.8)	TT	3 (23.1)	TT	2 (15.4)
*1/*3	1 (7.7)	CC	1 (7.7)	CT	3 (23.1)
*1/*4	4 (30.8)	ABCB1 G2677T/A genotypes	n (%)		
*1/*5	1 (7.7)	GT	7 (53.8)		
*1/*6	0 (0.0)	GG	3 (23.1)		
*4/*4	0 (0.0)	AT	2 (15.4)		
		TT	1 (7.7)		
CYP2D6 predicted phenotype	n (%)	CYP3A4 predicted phenotype	n (%)		
UM	0 (0.0)	UM	0 (0.0)		
EM	7 (53.8)	EM	11 (84.6)		
EM-IM	5 (38.5)	IM	2 (15.4)		
IM	1 (7.7)	PM	0 (0.0)		
PM	0 (0.0)				

**Notes:** CYP2D6, CYP3A4 and ABCB1 genotype and phenotype distributions were assessed in dextromethorphan group. NR1I2 genotype was assessed in memantine group. The CYP2D6 phenotype predicted from genotype was predicted as follows: UM if \*1/\*xN; EM if \*1/\*1; EM-IM if \*1/\*4, \*1/\*3 or \*1/\*6; IM if \*1/\*5 and PM if \*4/\*4.

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