ANESTHESIOLOGY

# Dextromethorphan Analgesia in a Human Experimental Model of Hyperalgesia

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Neuropathic pain, which presents abnormal pain manifestations including allodynia and hyperalgesia, is associated with central sensitization involving *N*-methyl-D-aspartate receptors
- In the freeze-injury hyperalgesia model, a cold burn leads to development of both primary hyperalgesia and secondary hyperalgesia, which develops away from the site of injury without apparent tissue modification, and is associated with central sensitization and activation of *N*-methyl-D-aspartate receptors in the spinal cord
- Dextromethorphan, which is an *N*-methyl-D-aspartate receptor antagonist, is antihyperalgesic in preclinical pain models

### What This Article Tells Us That Is New

- Using the freeze-injury pain model in a randomized, double-blind, placebo-controlled crossover trial of 30-mg doses of oral dextromethorphan in 20 male volunteers, dextromethorphan was antihyperalgesic and reversed peripheral and central neuronal sensitization
- Because dextromethorphan had no intrinsic antinociceptive effect in acute pain on healthy skin, *N*-methyl-D-aspartate receptors may need to be sensitized by pain for dextromethorphan to be effective

## ABSTRACT

**Background:** Central pain sensitization is often refractory to drug treatment. Dextromethorphan, an *N*-methyl-D-aspartate receptor antagonist, is antihyperalgesic in preclinical pain models. The hypothesis is that dextromethorphan is also antihyperalgesic in humans.

**Methods:** This randomized, double-blind, placebo-controlled, crossover study explores the antihyperalgesic effect of single and repeated 30-mg dose of oral dextromethorphan in 20 volunteers, using the freeze-injury pain model. This model leads to development of primary and secondary hyperalgesia, which develops away from the site of injury and is associated with central sensitization and activation of *N*-methyl-D-aspartate receptor in the spinal cord. The primary outcome was antihyperalgesia calculated with the area under the curve of the percentage change in mechanical pain threshold (electronic von Frey) on the area of secondary hyperalgesia. The secondary outcomes were mechanical pain threshold on the area of primary hyperalgesia and cognitive (reaction time) effect.

**Results:** Single 30-mg results are reported. Antihyperalgesia (% · min) is significantly higher on the area of secondary hyperalgesia with dextromethorphan than placebo (median [interquartile range]: 3,029 [746; 6,195] *vs.* 710 [–3,248; 4,439], $P = 0.009$, Hedge's g = 0.8, 95% CI [0.1; 1.4]). On primary hyperalgesia area, mechanical pain threshold 2 h after drug intake is significantly higher with dextromethorphan ($P = 0.011$, Hedge's g = 0.63, 95% CI [0.01; 1.25]). No difference in antinociception is observed after thermal painful stimuli on healthy skin between groups. Reaction time (ms) is shorter with placebo than with dextromethorphan (median [interquartile range]: 21.6 [–37.4; 0.1] *vs.* –1.2 [–24.3; 15.4], $P = 0.015$, Hedge's g = 0.75, 95% CI [0.12; 1.39]). Nonserious adverse events occurrence (15%, 3 of 20 volunteers) was similar in both groups.

**Conclusions:** This study shows that low-dose (30-mg) dextromethorphan is antihyperalgesic in humans on the areas of primary and secondary hyperalgesia and reverses peripheral and central neuronal sensitization. Because dextromethorphan had no intrinsic antinociceptive effect in acute pain on healthy skin, *N*-methyl-D-aspartate receptor may need to be sensitized by pain for dextromethorphan to be effective.

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Neuropathic pain, defined as pain caused by a lesion or a disease of the somatosensory nervous system,[1] affects 7 to 10% of the general population[2] and is associated with central sensitization involving *N*-methyl-D-aspartate (NMDA) receptors.[3] Neuropathic pain presents abnormal pain manifestations including allodynia and hyperalgesia[1] and is accompanied by impaired quality of life. Management of neuropathic pain is still not satisfactory[4] and in recent years, special attention has been focused on NMDA receptor antagonists, ketamine, memantine, and

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dextromethorphan. The analgesic mechanism of action of dextromethorphan, mainly used as a cough suppressant with safety hazards,[5] remains incompletely known, however.

A preclinical study in a spinal nerve ligation animal model showed that postsurgical dextromethorphan administration induced a significant decrease of allodynia and hyperalgesia while preserving mobility and cognition in the Y-maze test.[6] These positive findings in animals and in some clinical studies showing neuropathic pain alleviation after trauma[7,8] and diabetes,[9] although not universal,[10,11] triggered an ongoing clinical trial (NCT02271893)[12] in patients with refractory postsurgery neuropathic pain and central pain sensitization. To complement this translational approach, human experimental pain models may mimic some neuropathic pain characteristics and central pain sensitization, and help to understand the pharmacology of dextromethorphan. In the freeze-injury hyperalgesia model, a cold burn leads to the development of primary hyperalgesia,[13] and of secondary hyperalgesia that develops away from the site of injury without apparent tissue modification, and is associated with central sensitization, rather than neuropathic pain *per se*, and activation of NMDA receptor in the spinal cord.[14] Such an experimental model has not been used so far with dextromethorphan and might allow a better understanding of the antinociceptive effect of dextromethorphan in pain central sensitization.

Dextromethorphan is known to bind noncompetitively with low-moderate affinity to the phencyclidine site in the NMDA receptor channel.[15] It also has a moderate-affinity agonist activity with σ1 receptor sites and is an antagonist of nicotinic acetylcholine receptors. It is metabolized by cytochrome P450 (CYP), CYP2D6, to dextrorphan, its main active metabolite, and by CYP3A4 to inactive metabolites.[16] Genetic polymorphism may be a variability factor of dextromethorphan metabolism (*CYP2D6, CYP3A4*), efflux (P-glycoprotein encoded by *ABCB1* gene),[17–19] and analgesic effect.[7,8] This analgesic effect has been attributed to dextromethorphan itself[8] or to dextrorphan.[7] Dextromethorphan has also an impact on cognition[20] and has been considered as an opioid, although some publications rather suggest a nonopioid effect[21,22] (inhibitory constant for dextromethorphan: 1,280 nM; inhibitory constant for dextrorphan: 420 nM).[23] Its role on the autonomic nervous system is still unclear.[24] These characteristics may be assessed respectively by cognitive tests and by pupillometry, as miosis—a known effect of opioids—pupil size and reactivity to light, reflect the iris autonomic nervous system.[25]

Using the freeze-injury–induced hyperalgesia model, this placebo-controlled study aims to explore the antihyperalgesic effect of single and repeated doses of 30-mg dextromethorphan with mechanical painful stimuli, central activity (reaction time and pupillary diameter), and metabolism (drug measurements) in healthy volunteers.

## Materials and Methods

This randomized, double-blind, placebo-controlled and crossover study was conducted in the Clinical Pharmacology Department and Clinical Research Center, University Hospital of Clermont-Ferrand, Clermont-Ferrand, France, from November 2015 to February 2016. It was approved by the referent ethics committee CPP (Committee for the Protection of Persons) Sud-Est VI, Clermont-Ferrand, France, (AU1213) and the French competent authority (151147A-32). It was registered on EudraCT (2015-003171-30) and ClinialTrials.gov (NCT02596360).

### Subjects

Subjects were preselected from the Healthy Volunteers File of the Clinical Pharmacology Department and Clinical Research Center. All subjects were compensated for their participation in the study.

Caucasian healthy male volunteers were eligible if they were between 18 and 45 yr old, with a body mass index of at least 19 and no greater than 30 kg/m$^2$, were extensive or intermediate CYP2D6 metabolizers, as determined during the prescreening visit, and were required to be free of any medication for at least 7 days before inclusion. Volunteers were excluded with a known hypersensitivity to dextromethorphan, aspartate transaminase, alanine transaminase and total bilirubin twice the normal range, consumption of alcohol, tobacco, or any drug addiction. In order to avoid interfering with the psychometric tests results, volunteers were asked not to consume magnesium, citrus juice, drinks with theine, or caffeine during the assessment days. Volunteers lacking concentration and not able to evaluate pain thresholds were excluded. Eligible volunteers were informed about the protocol and provided a signed informed consent before inclusion.

### Study Design

After inclusion, volunteers were familiarized (one session) with the psychophysics experiments. Blood samples were collected from all participants to assay serum aspartate transaminase, alanine transaminase, and bilirubin levels, *CYP2D6*, *CYP3A4*, and *ABCB1* genotyping. The selected volunteers were randomly assigned to receive oral dextromethorphan bromhydrate tablets (Pulmodexane 30 mg [23 mg dextromethorphan base]; Bailly-Creat Laboratory, France, maximal dose 120 mg daily) or placebo similar in appearance to dextromethorphan tablets (lactose, Cooper Laboratory, France) in two randomized periods 11 days apart according to a randomization list. The randomization sequence was generated using random blocks and was established beforehand by a research assistant who was not involved in the trial. Volunteers and all personnel involved in the trial conduct were blinded to the treatment assignment.

On day 0, after freeze injury induction, volunteers had baseline tests ($t_0$) and received 30 mg of dextromethorphan or placebo. Treatment was given by a nurse independent of the study. Tests were repeated at 1 h, 2 h, and 3 h to assess the effects of a single dose. Thereafter, to measure the effects of drugs after repeated dosages, while respecting the maximal

dosage recommendations, volunteers took 30 mg of dextromethorphan or placebo four times at home: three times on day 0 (5 h, 10 h, and 14.5 h after baseline) and once on day 1 (22.5 h after baseline). Tests were repeated on day 1. After a washout period of 11 days, the same procedure was repeated in a crossover fashion during the second session starting at day 13 and ending at day 15. Drug adverse events were collected during the sessions by a nurse independent of the study on day 0 and day 14 between the third and the fourth dextromethorphan doses and during the washout period. A detailed overview of the experimental design is given on figure 1.

## Experimental Pain Model Induction

In the majority of human pain models,[26] the induced hyperalgesia is dose-dependent, is not reproducible, is not stable with time, and does not last long enough (1–3 h with capsaicin and mustard oil) to cover the duration of action of repeated drug administration. In this present study, the freeze-injury–induced hyperalgesia model described by Kilo *et al.*[13] was chosen to induce reproducible primary and secondary hyperalgesia that may stay stable for 72 h[13,27] with the absence of carryover effect as described previously.[27] This experimental cutaneous hyperalgesia model consists

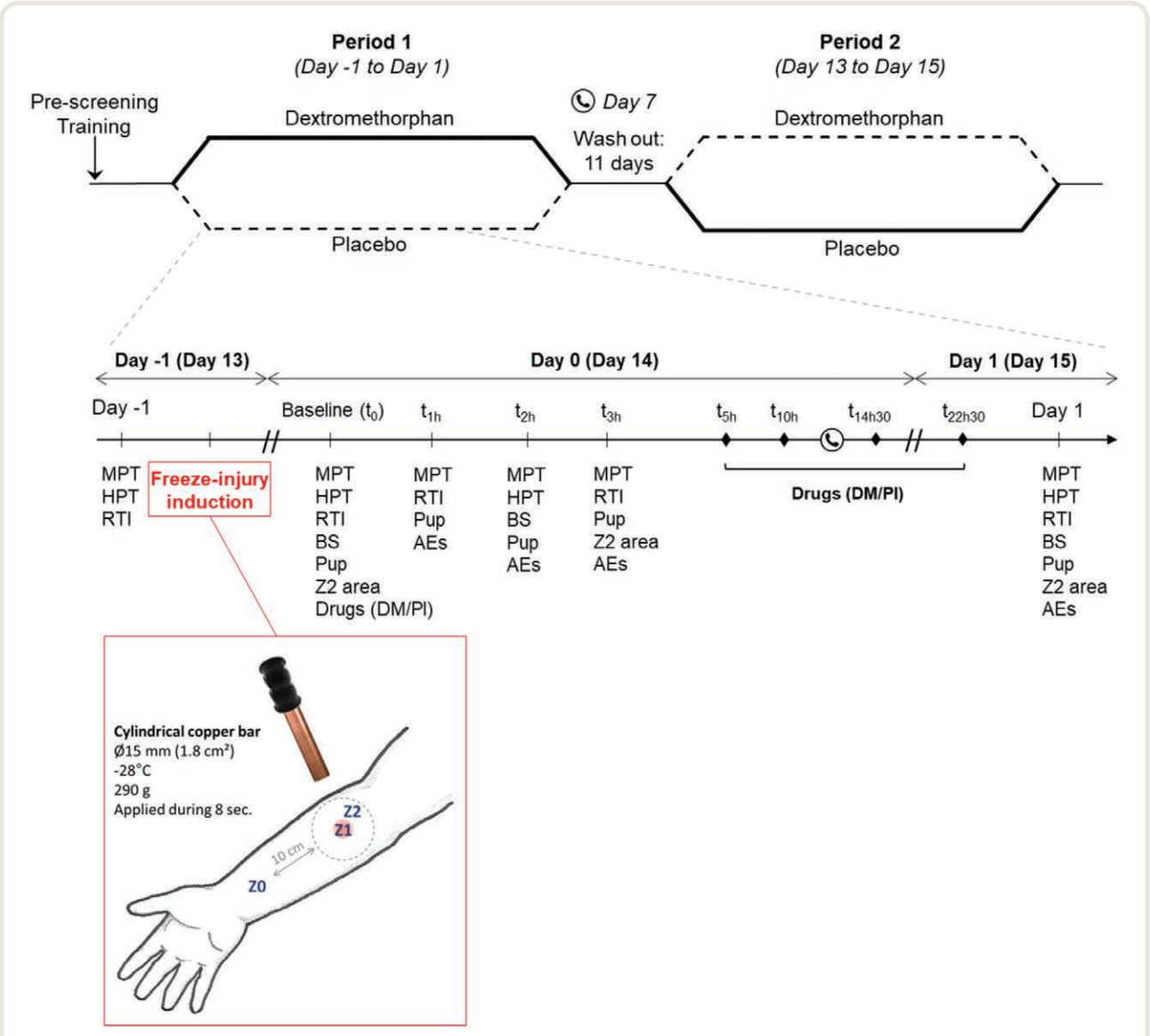


**Fig. 1.** Design and chronology of the study. AEs, adverse events; BS, blood sample; DM/PI, dextromethorphan or placebo administration; HPT, heat pain thresholds; MPT, mechanical pain thresholds; Pup, pupillometry; RTI, reaction time Cambridge Neuropsychological Test Automated Battery test; $t_{1h}$, 1 h after baseline; $t_{2h}$, 2 h after baseline; $t_{3h}$, 3 h after baseline; $t_{5h}$, 5 h after baseline; $t_{10h}$, 10 h after baseline; $t_{14h30}$, 14.5 h after baseline; $t_{22h30}$, 22.5 h after baseline; Z0, healthy skin; Z1, primary hyperalgesia; Z2, secondary hyperalgesia; Z2 area, secondary hyperalgesia surface measurement.

of applying for 8 s on the anterior glabrous part of the forearm (dominant arm in the first study period and nondominant arm in the second) the tip of a 15-mm-diameter and 290-g-weight cylindrical copper bar frozen at –28°C. The induced first-degree burn leads to two types of hyperalgesia: a primary hyperalgesia area associated with a sharply defined erythema, corresponding to the surface in contact with the copper bar, and a localized secondary hyperalgesia area surrounding primary hyperalgesia in undamaged skin (fig. 1).[13] A control skin area was determined on the injured arm at a distance of 20 cm from the lesion.

The primary endpoint was the comparison of the areas under the curve (AUC) of the percentage change in mechanical pain threshold (% MPT, providing force to 0.1 g) between baseline and 3 h after drug intake (AUC $\%MPT_{t0\text{-}t3h}$; % · min) in the secondary hyperalgesia area between dextromethorphan *versus* placebo according to the formula

$$AUC\%MPT_{t0\text{-}t3h}\ (\% \cdot \min) = 60 \times ((((t_{1h} - t_0) \times 100) / t_0) + (((t_{2h} - t_0) \times 100) / t_0)) / 2 + 60 \times ((((t_{2h} - t_0) \times 100) / t_0) + (((t_{3h} - t_0) \times 100) / t_0)) / 2,$$

with $t_0$, $t_{1h}$, $t_{2h}$, and $t_{3h}$ corresponding to mechanical pain threshold at baseline, 1 h, 2 h, and 3 h after drug, respectively.

Secondary outcome measures were the assessment of mechanical pain threshold in primary hyperalgesia and healthy skin areas, the evolution of the secondary hyperalgesia area, thermal pain thresholds, pupillary reactivity, cognitive status, plasma dextromethorphan and dextrorphan concentrations, and drug adverse events.

## Procedures of Pain Assessment

*Mechanical Test.* The electronic von Frey (Somedic, France) test consists in applying pressure with a 0.2-mm-diameter probe tip on the middle of primary hyperalgesia, secondary hyperalgesia, and control skin areas with a constant slope of increasing punctate pressure up to the detection of mechanical pain thresholds (grams), corresponding to the first pain sensation, signaled by the volunteer by a response push button. The mean of three measurements was taken as the mechanical pain threshold. An increase of mechanical pain threshold signifies that the individuals cope better with pain.

*Secondary Hyperalgesia Area Measurement.* The borders of the secondary hyperalgesia area were determined with a handheld 588-mN von Frey hair by concentric stimulations along six linear paths arranged radially around the lesioned site. When the volunteer reported a clear change in sensation, this was defined as the border of the secondary hyperalgesia area. Secondary hyperalgesia areas ($cm^2$) were calculated with the software ImageJ[28] (W.S. Rasband, M.Sc., U.S. National Institutes of Health, Bethesda, Maryland; ImageJ, https://imagej.nih.gov/ij/). Primary hyperalgesia area was defined as the area of erythema corresponding to the skin area in contact with the frozen copper bar (1.8 $cm^2$).

*Thermal Tests.* Heat pain threshold was assessed using the Advanced Thermal Stimulator thermode (30 × 30 mm) connected to the Medoc Pathway system (Medoc Ltd., Israel) applied on normal skin of the control arm. From the baseline value of 32°C, the Medoc Pathway system delivers an adjustable temperature peak in heat with a slope increase of 1°C increments and controlled by rapid feedback. Heat pain threshold was determined as the mean of three measures.

## Evaluation of Central and Cognitive Effects of Dextromethorphan

*Pupillary Reactivity Measurement.* Pupillometry recordings were performed with a noninvasive monocular portable infrared pupillometer (NeuroLight Algiscan; IDMED, France) to measure a baseline scotopic pupil size (mm), then quantitative pupillary light reflex, which represents the reduction in pupil size after light stimulation. Scotopic conditions were obtained with the device's light-tight occlusive silicone collar between the camera and the edges of the orbit and with the subject shielding his contralateral eye tightly with a hand. After application, the subject was asked to keep the eye open, and pupil diameter was noted after stable values were obtained (30 s in general). All measurements were undertaken on the right pupil, or on the left in case of abnormality of the right eye.

*Reactivity Measurement.* Reaction time, measured to 0.1-ms precision, was assessed using the Cambridge Neuropsychological Test Automated Battery (Cambridge Cognition, United Kingdom). Reaction time (ms) is the time taken to release the press pad in response to the visual stimulus (yellow dot). Movement time (ms) is the time taken to touch the yellow dot on the touchscreen after the press pad has been released. Differences from baseline (delta) were compared between dextromethorphan and placebo.

## Pharmacogenetics and Plasma Concentrations

Considering genetic polymorphism in dextromethorphan effect, CYP2D6 extensive and intermediate metabolizer volunteers have been selected in this study to homogenize the population on this highly polymorphic enzyme. Interindividual variations in the disposition of dextromethorphan/dextrorphan have been investigated.

Genomic DNA samples, collected during the prescreening visit, were extracted from blood mononuclear cells by use of a commercial kit (Maxwell 16 LEV Blood DNA Kit, Promega, France) according to the manufacturer's protocols.

*CYP2D6 Genotyping.* The *CYP2D6*6* allele was detected by use of the long polymerase chain reaction method for the whole-gene amplification, followed by a subsequent nested polymerase chain reaction and restriction enzyme analysis.[29] Gene deletion (*CYP2D6*5* allele) and gene duplication (responsible for ultrarapid phenotype) were analyzed by the long polymerase chain reaction method as previously described.[30] *CYP2D6*3, CYP2D6*4*, and *CYP2D6*6*

were detected by use of Taq Man Drug Metabolism Genotyping Assays (C__32407232_50, C__27102431_Day 0, C__32407243_20; Applied Biosystems-Thermo Fisher Scientific, France).

*Dextromethorphan and Dextrorphan Plasma Concentrations.* Plasma concentrations were quantified after acetonitrile precipitation using a validated high-performance liquid chromatography tandem mass spectrometry method (TSQ Quantum Ultra, Fisher, USA). Separation was carried out on an Accucore Phenyl Hexyl column (100 mm × 2.6 mm, 2.6 μm, Fisher). The mobile phase consisted of solvent A (0.1% formic acid in water) and solvent B (0.1% formic acid in acetonitrile) with gradient program. Briefly, aliquots of plasma (200 μl) were added to 100 μl of internal standard (dextrorphan-d3, 200 ng/mL, LGC, United Kingdom) and 600 μL of acetonitrile. After centrifugation and evaporation of organic phase under nitrogen flow at 30°C, the residue was dissolved in 100 μL of water/methanol (95/5%) with 0.1% formic acid and 10 μl used for injection.

Detection in triple quadrupole mass spectrometry used an electrospray ionization probe and operated in the positive ion mode. The multiple reaction monitoring transitions used for quantification were 272.1/215.0 for dextromethorphan, 258.1/201.1 for dextrorphan, and 261.1/157.1 for dextrorphan-d3. The linear calibration ranges in plasma (correlation coefficients greater than 0.999) were 2.5 to 250 ng/ml for dextromethorphan and 1 to 500 ng/ml for dextrorphan. The metabolic ratio was calculated by dividing dextrorphan concentration by dextromethorphan concentration.

## Statistical Analysis

For type I and type II errors of 5% (two-sided) and 20%, respectively, and with intraindividual correlation coefficient equals to 0.5 (owing to the crossover design and no carryover effect assumed), 19 patients are needed to highlight a difference of at least 3,400 on the primary outcome for an effect size around 0.70. This primary outcome is the area under the curve of the percentage change in mechanical pain threshold between baseline and 3 h after drugs intake (AUC $\%MPT_{t0\text{-}t3h}$) in secondary hyperalgesia after treatment administration (with a SD of 4,900), according to the study results previously detailed in the literature.[26] According to these estimations, 20 patients were included per group.

Statistical analysis was performed using the Stata software (Version 13, StataCorp, USA) where hypothesis testing was two-sided with significance interpreted as $P < 0.05$. For continuous parameters, mean ± SD or median and interquartile range were calculated, according to statistical distribution. The Shapiro–Wilk test was used to study normality assumption of continuous data. Then, the primary endpoint and secondary endpoints were compared between groups using a random-effects model for crossover designs while taking into account the following effects: treatment group, sequence, subject (as random-effect), and carryover. A Sidak's type I error correction was applied to take into account the multiple comparisons. The normality of residuals was studied using the Shapiro–Wilk test when appropriate, and a logarithmic transformation has been proposed to achieve the normality. The results were expressed using Hedges's g effect size and 95% CI. For categorical parameters, a Stuart–Maxwell test for paired data or generalized linear mixed model (binomial distribution with log link for dichotomous endpoint) was applied. Random effect models were also carried out to analyze repeated measures to study fixed effects (group, timepoints and interaction group × time). A cumulative proportion of responder's analysis (AUC $\%MPT_{t0\text{-}t3h}$, 0, 1,000, 2,000, 6,000, 10,000, 12,000, 14,000, 16,000) comparing dextromethorphan to placebo was performed to provide a visual representation of the likelihood of response over a full range of response levels for the two groups. The analysis was conducted using random effects model to measure group and response level effects and their interaction, taking into account between- and within-subject variability.

Concerning noncrossover comparisons, usual statistical tests were performed: independent Student's *t* test or Mann–Whitney test (when assumptions of *t* test were not met: normality and homoscedasticity) for quantitative parameters and chi-square test or Fisher exact test for categorical variables. The Kruskal–Wallis test and Spearman correlation coefficient (rather than Pearson correlation due to non-Gaussian statistical distribution) was used to identify relations between dextromethorphan and dextrorphan plasma concentrations, pain, central, and cognitive parameters.

# Results

## Study Subjects

For this study, 34 healthy males were prescreened, 23 were randomized, 3 were excluded from the analysis (consent withdrawal, unstable pain model, and flu-like syndrome), and 20 volunteers were analyzed. The flowchart is presented in figure 2.

## Characteristics of Induced Hyperalgesia

*Stability of the Pain Model with Time and Induced Hyperalgesia.* At baseline, a significant decrease of the mechanical pain threshold in primary and secondary hyperalgesia ($P < 0.001$, effect size = –0.81 [–1.26; –0.36]) was observed when compared to control skin area (measured before the pain model induction) in both treatment groups. With the placebo, the freeze-injury–induced hyperalgesia was maintained (comparison *vs.* control skin) in primary hyperalgesia at each timepoint in day 0 and day 1 ($P < 0.001$, effect size = –1.02 [–1.67; –0.37]), and in secondary hyperalgesia at each time at day 0, 1 h after dosing

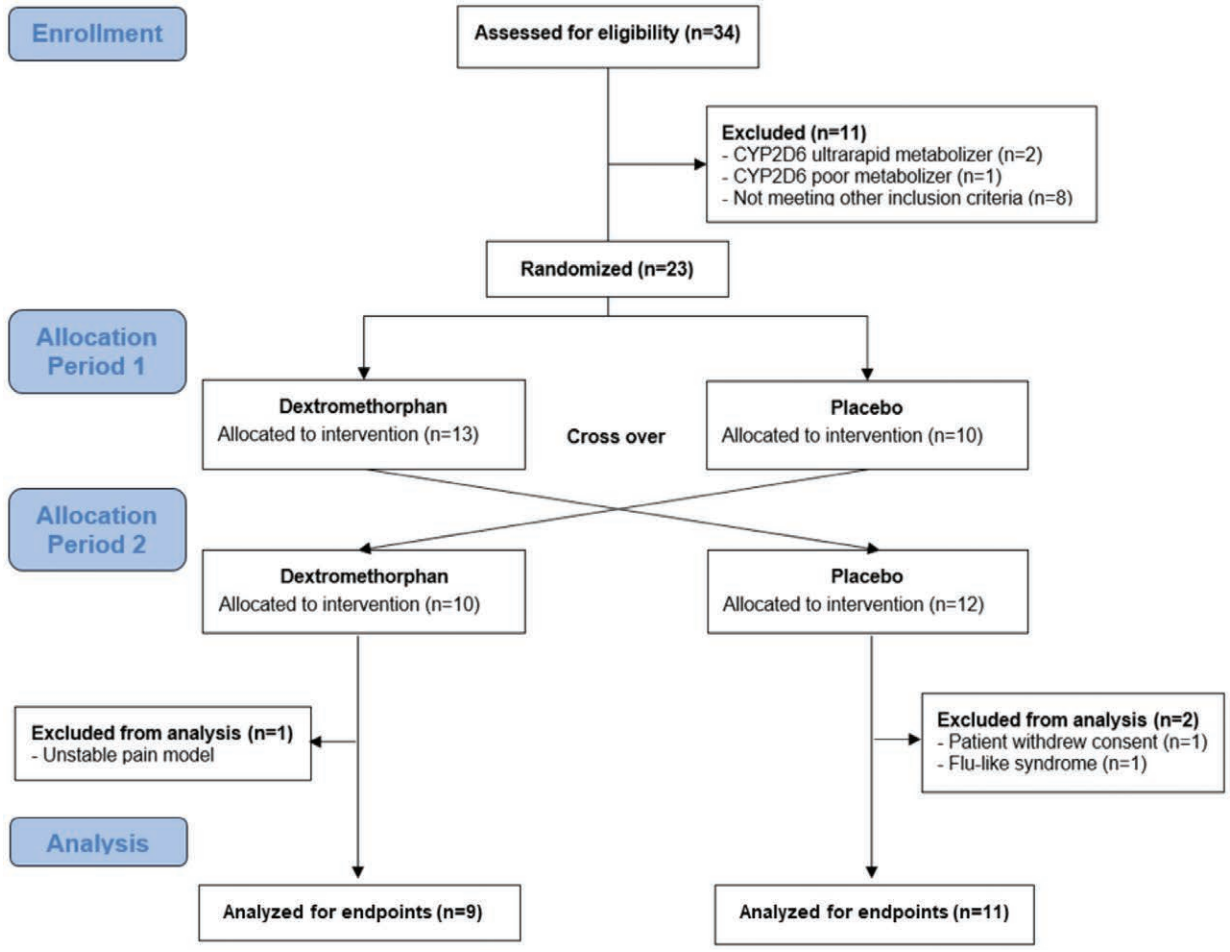


**Fig. 2.** Flowchart of participants during the trial.

($P < 0.001$, effect size = –0.82 [–1.46; –0.18]), 2 h after dosing ($P < 0.001$, effect size = –0.83 [–1.47; –0.19]), 3 h after dosing ($P < 0.001$, effect size = –0.70 [–1.66; –0.04]) but for only 10 out of 20 individuals (50%) at day 1 ($P = 0.069$, effect size = –0.37 [–0.99; 0.25]).

*Primary Study Endpoint.* Evaluation of secondary hyperalgesia shows on day 0, between 1 and 3 h after dosing, a significant increase of the area under the curve of the percentage change in mechanical pain threshold ($AUC\%MPT_{t0\text{-}t3h}$) between dextromethorphan compared to placebo ($P = 0.009$, effect size = 0.8 [0.1; 1.4]; table 1). The cumulative proportion of responder's analysis, comparing dextromethorphan to placebo, provides a statistically significant proportion of responders ($P < 0.001$). More precisely, the significance of $AUC\ \%MPT_{t0\text{-}t3h}$ is $P = 0.003$ (proportion of responders = 85% *vs.* 45%) at level 0 and $P = 0.011$ (proportion of responders = 75% *vs.* 40%; fig. 3) at level 1,000. From $t_0$ to day 1, the surface of secondary hyperalgesia shrank concentrically toward primary hyperalgesia, and this was not significantly different between dextromethorphan and placebo at $t_0$ ($P = 0.625$, effect size = 0.2 [–0.5; 0.8]), at 3 h after dosing ($P = 0.991$, effect size = 0.0 [–0.6; 0.6]) and at day 1 ($P = 0.743$, effect size = 0.1 [–0.5; 0.7]; table 1). Raw values of mechanical pain thresholds in secondary hyperalgesia, primary hyperalgesia and healthy skin are shown in Supplemental Digital Content 2 (http://links.lww.com/ALN/B949).

*Primary Hyperalgesia.* Mechanical pain thresholds (delta) on primary hyperalgesia increased significantly for dextromethorphan compared to placebo between $t_0$ and $t_{1h}$ ($delta_{t0\text{-}t1h}$, dextromethorphan: 4.6 ± 11.6 g, placebo: –3.6 ± 17.6 g, $P = 0.038$, effect size 0.53 [0.09; 1.15]), between baseline and 2 h after dosing ($delta_{t0\text{-}t2h}$, dextromethorphan: 7.9 ± 12.8 g, placebo: –2.8 ± 19.7 g, $P = 0.011$, effect size 0.63 [0.01; 1.25]) and between baseline and day 1 ($delta_{t0\text{-}day1}$, dextromethorphan: 8.4 ± 15.6 g, placebo: –2.9 ± 21.1 g, $P = 0.015$, effect size 0.60 [0.03; 1.27]). The primary hyperalgesia surface did not change during the entire study period.

**Table 1.** Effect of Dextromethorphan on Primary and Secondary Outcome Measures

| | Dextromethorphan (n = 20) | Placebo (n = 20) | *P* Value |
|---|---|---|---|
| $AUC\%MPT_{t0\text{-}t3h}$ (% · min) | | | |
| | 3,029 [746; 6,195] | –710 [–3,248; 4,439] | 0.009 |
| Secondary hyperalgesia surface ($cm^2$) | | | |
| $t_0$ | 42.65 ± 18.79 | 39.86 ± 18.26 | 0.625 |
| $t_{3h}$ | 29.45 ± 19.49 | 29.38 ± 17.84 | 0.991 |
| Day 1 | 23.12 ± 19.30 | 21.55 ± 15.92 | 0.743 |
| Heat pain thresholds (°C) | | | |
| $t_0$ | 42.1 ± 2.3 | 42.5 ± 1.7 | 0.313 |
| $t_{2h}$ | 42.4 ± 2.3 | 42.6 ± 2.0 | 0.631 |
| Day 1 | 43.4 ± 1.9 | 43.3 ± 1.6 | 0.819 |
| Movement time, delta from baseline (ms) | | | |
| $t_{1h} – t_0$ | 28.6 [–37.6; 108.4] | –26.5 [–71.5; 53.1] | 0.229 |
| $t_{3h} – t_0$ | 19.8 [–53.9; 105.9] | 10.3 [–69.5; 78.2] | 0.650 |
| Day 1 – $t_0$ | –29.6 [–66.2; 53.3] | –47.2 [–86.0; 47.6] | 0.518 |
| Pupillary light reflex (%) | | | |
| $t_0$ | 40 ± 5 | 40 ± 4 | 0.921 |
| $t_{1h}$ | 40 ± 5 | 40 ± 4 | 0.959 |
| $t_{2h}$ | 39 ± 5 | 39 ± 5 | 0.847 |
| $t_{3h}$ | 39 ± 5 | 39 ± 5 | 0.952 |
| Day 1 | 39 ± 5 | 39 ± 5 | 0.639 |

Effect of dextromethorphan on mechanical pain threshold in secondary hyperalgesia (area under the curve of the percentage change in mechanical pain threshold in secondary hyperalgesia [$AUC\%MPT_{t0\text{-}t3h}$]), secondary hyperalgesia surface, heat pain thresholds, movement time, and pupillary light reflex (mean ± SD or median [interquartile range]).

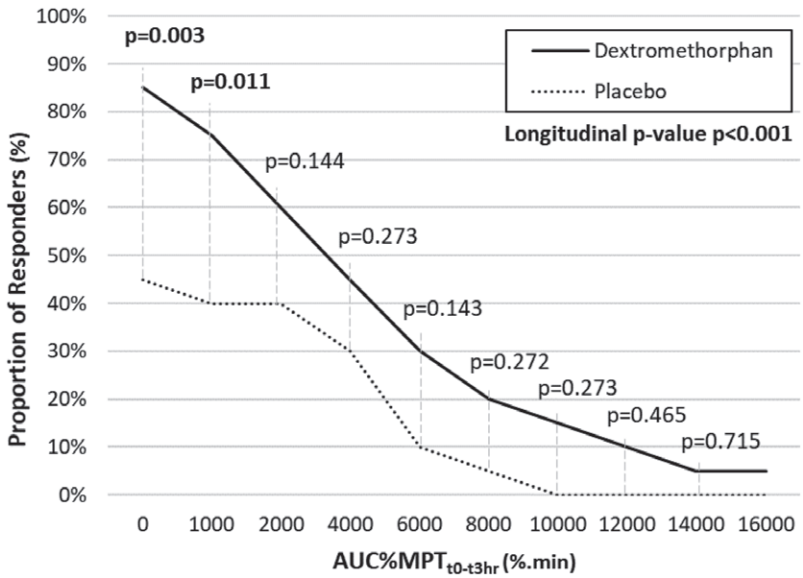


**Fig. 3.** Cumulative proportion of responder's analysis with area under the curve of the percentage change in mechanical pain threshold in secondary hyperalgesia ($AUC\%MPT_{t0\text{-}t3h}$ >0; %.min) in dextromethorphan and placebo groups. A statistically significant proportion of responders ($P < 0.001$) was observed, more precisely at AUC $\%MPT_{t0\text{-}t3h}$ level 0 $P = 0.003$ and level 1,000 $P = 0.011$. *P* values were estimated applying a Sidak's correction type I error.

*Thermal Thresholds.* No significant difference was observed between treatments in heat pain threshold on the control skin area on the opposite arm of the freeze-injured arm (table 1).

## Cognitive Parameters

With the placebo, repeated reaction time decreased compared to baseline, suggesting a learning process. This diminution was

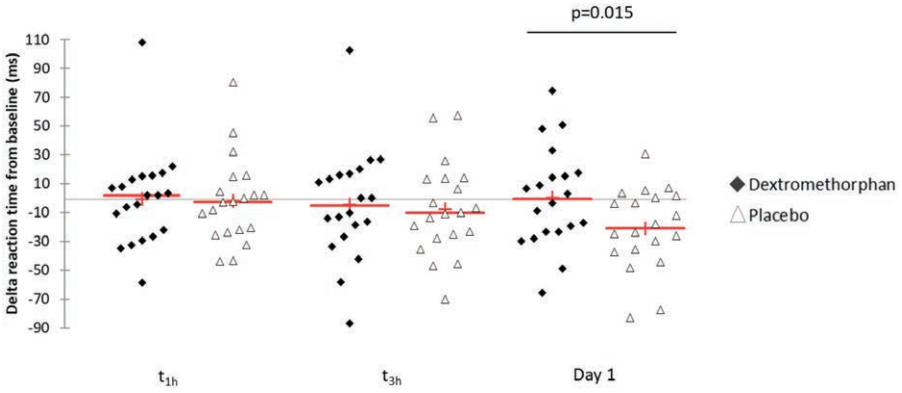


**Fig. 4.** Effect of dextromethorphan on reaction time. With placebo, reaction time decreased compared to baseline, suggesting a learning process that was not observed with dextromethorphan. Delta reaction time between baseline and Day 1 was larger with dextromethorphan than with placebo ($P = 0.015$). The *plus sign* and the *straight line* represent, respectively, the mean and the median of values. *P* values were estimated applying a Sidak's correction type I error. $t_{1h}$, 1 h after baseline; $t_{3h}$, 3 h after baseline.

not observed with dextromethorphan, and the repeated test showed that delta reaction time between baseline and day 1 was larger with dextromethorphan than with placebo ($P = 0.015$, effect size = 0.75 [0.12; 1.39]; fig. 4). No significant difference between treatments was observed in movement time at any time, but variability was very high (table 1). Raw values of reaction time and movement time are shown in Supplemental Digital Content 2 (http://links.lww.com/ALN/B949).

### Pupillary Reactivity

Two hours after drugs intake ($t_{2h}$), corresponding to the plasmatic peak of dextromethorphan,[31] a significant difference of pupil diameter was observed between treatments with a larger diameter for dextromethorphan compared to placebo ($P = 0.017$, effect size = 0.49 [0.06; 0.94]; fig. 5A). No significant difference was observed between treatments concerning pupillary light reflex (table 1).

### Pharmacogenetics and Plasma Concentrations

The study was designed with a homogenous population by selecting extensive or intermediate CYP2D6 metabolizers. Correlations between concentrations of dextromethorphan and dextrorphan, hyperalgesia, central, and cognitive parameters have been studied. At day 1, there was a positive significant correlation between dextrorphan concentration and reaction time ($\rho = 0.715$, $P = 0.001$). A negative significant correlation was observed between metabolic ratio and pupillary diameter change 2 h after dosing ($\rho = -0.559$, $P = 0.012$; fig. 5B). A negative correlation was observed for dextrorphan concentration ($\rho = -0.267$) and a positive correlation with dextromethorphan concentration ($\rho = 0.225$; fig. 5B). Concentrations of dextromethorphan and dextrorphan at day 0 (dextromethorphan: 1.7 ± 1.6 ng/ml, 95% CI [1.0; 2.4]; dextrorphan: 3.4 ± 1.5 ng/ml, 95% CI [2.7; 4.0]) and at day 1 (dextromethorphan: 3.8 ± 5.5 ng/ml, 95% CI [1.4; 6.2]; dextrorphan: 6.5 ± 2.8 ng/ml, 95% CI [5.3; 7.8]) are shown in Supplemental Digital Content 1 (http://links.lww.com/ALN/B948).

### Adverse Events

The proportion of subjects experiencing possible drug-related nonserious adverse events was 15% (3 of 20 volunteers) with both dextromethorphan and placebo treatments ($P > 0.999$). With dextromethorphan, adverse events were of mild severity and were those commonly reported for this drug (dry mouth, fatigue, n = 3). With the placebo, subjects experienced fatigue and stomach ache (n = 3). No serious adverse event was reported.

## Discussion

This study in healthy volunteers shows in humans that low-dose (30 mg) oral dextromethorphan significantly diminishes hyperalgesia in a freeze-injury pain model, whereas previous studies mainly assessed this effect in animals or with higher dosages in humans (*e.g.*, 270 mg[7]; 960 mg/day[32]). The secondary hyperalgesia induced by the model was significantly decreased ($P = 0.009$), confirming the antihyperalgesic effect of dextromethorphan. This is consistent with the literature reporting that NMDA receptor noncompetitive antagonists, by blocking the NMDA receptor channel, could limit or even reverse central sensitization symptoms.[6,33] The main mechanism of secondary hyperalgesia results from central neuronal sensitization mediated by low-threshold myelinated mechanoreceptors and nociceptors (stimulated by punctate hyperalgesia),[34,35] and descending facilitation of spinal nociception contributes to the maintenance of secondary hyperalgesia.[36]

The study also showed that dextromethorphan significantly reduced primary hyperalgesia to punctate stimuli ($P < 0.03$),

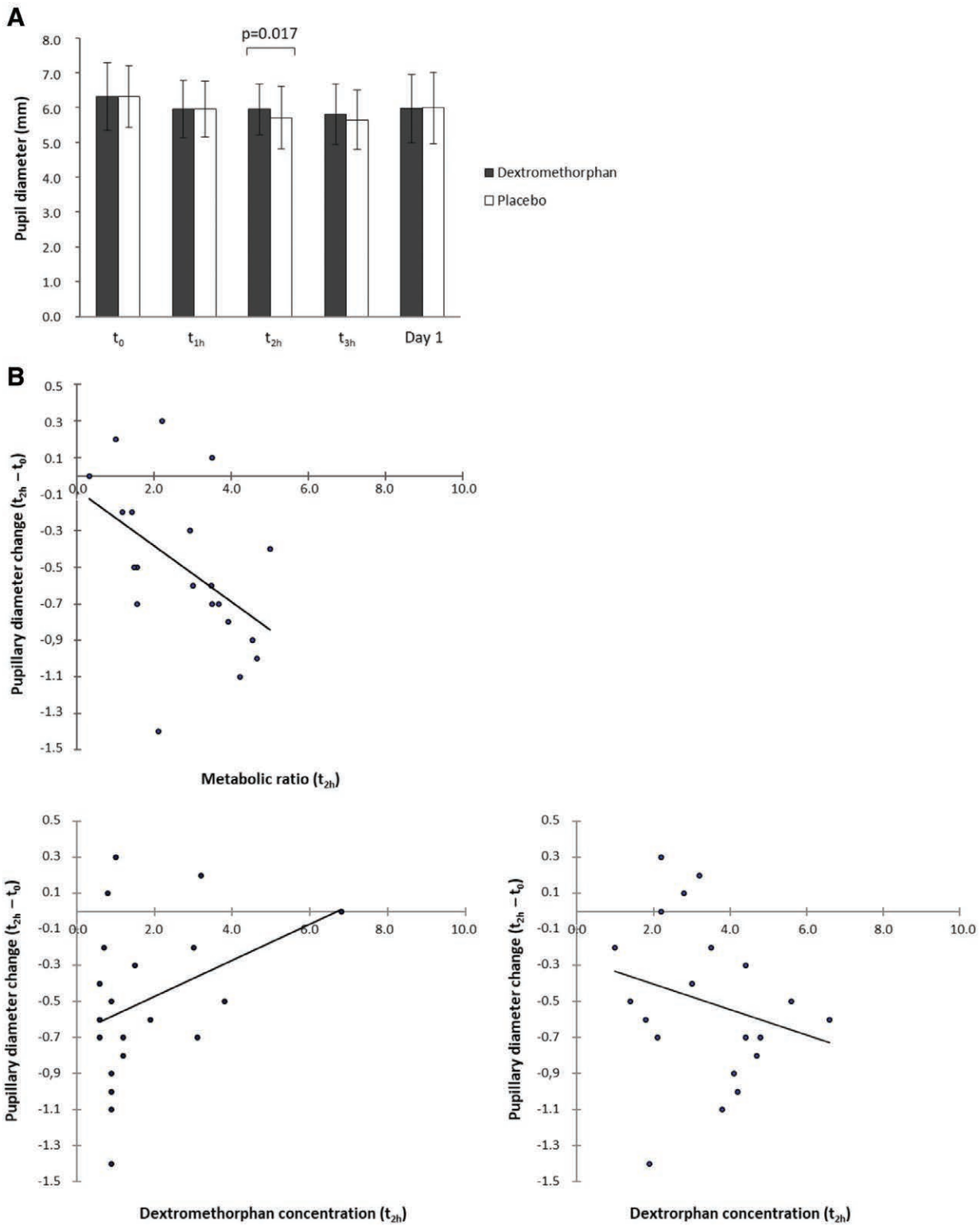


**Fig. 5.** Effect of dextromethorphan on basal pupillary diameter. (*A*) Two hours after dosing, a significant larger pupil diameter was observed with dextromethorphan compared to placebo ($P = 0.017$). (*B*) A negative significant correlation ($\rho = -0.559$, $P = 0.012$) was observed between pupillary diameter change (between 2 h after dosing and baseline) and metabolic ratio 2 h after dosing (metabolic ratio = dextrorphan/dextromethorphan). A positive correlation ($\rho = 0.225$, $P = 0.338$) and a negative correlation ($\rho = -0.267$, $P = 0.254$) were observed between pupillary diameter change (between 2 h after dosing and baseline) with dextromethorphan and dextrorphan, respectively. $t_0$, baseline; $t_{1h}$, i h after baseline; $t_{2h}$, 2 h after baseline; $t_{3h}$, 3 h after baseline.

possibly *via* blockade of voltage-gated sodium channels[37] or peripheral antiinflammatory action.[38,39] These findings underline the effectiveness of dextromethorphan on both central and peripheral sensitization with mechanical stimuli. Although dextromethorphan had a significant antihyperalgesic effect, the secondary and primary hyperalgesia surfaces diminished similarly with time for dextromethorphan and placebo, suggesting that dextromethorphan does not interfere with the spontaneous wound healing processes. Such an observation has not been reported in the literature, and skin biopsies could shed some light on this hypothesis. Concerning other pain modalities, while dextromethorphan had an effect on mechanical pain stimuli, it did not have any on acute thermal painful stimuli in healthy skin, confirming previous studies of a poor effect of dextromethorphan on thermal challenges.[40,41] This may suggest that dextromethorphan does not behave like an agonist of μ opioid receptors that are expressed in peptidergic pain fibers and regulate the heat pain responsiveness.[42]

Concerning the effect of dextromethorphan on pain, our sample included only CYP2D6 extensive or intermediate metabolizers. A pharmacogenetic approach,[8] including *CYP3A4* and *ABCB1* polymorphisms, needs to be explored further as dextromethorphan-induced analgesia is considered to be mediated by dextromethorphan[8] or by its metabolite dextrorphan.[7]

The study also explored the central effect of dextromethorphan by pupillometry, and a lesser constriction of the pupillary diameter was reported, (fig. 5A) as described in previous publications[43,44] that stressed the occurrence of mydriasis after dextromethorphan intake. Even though noradrenaline concentration was not measured, the mydriasis could be partly explained by the inhibition of noradrenaline reuptake[24] as suggested by the mydriatic effect of noradrenaline reuptake inhibitors like venlafaxine and reboxetin antidepressants.[45,46] Dextromethorphan and dextrorphan have been reported to inhibit *in vitro* noradrenaline uptake into rat brain with inhibitory constant values of 240 nM and 340 nM, respectively.[23] Another possible explanation is that dextromethorphan could behave as an α agonist (inhibitory constant = 3000 nM) [24]and directly dilate the radial muscles of the iris. It is well accepted that a decreased arousal of the central nervous system (often induced by sedation) is accompanied by miosis and that sedation is a well-known adverse event of dextromethorphan.[32] It is interesting to note that the pupillary light reflex remained stable in our study, underlining that the dosage of dextromethorphan (30 mg/day up to 120 mg/day) did not induce central nervous system depression. However, we observed a significant negative correlation between the change of pupil diameter and metabolic ratio, showing that larger dextrorphan concentrations might be correlated with a miosis (fig. 5B). We also observed a negative correlation for dextrorphan concentration ($\rho = -0.267$) and a positive correlation for dextromethorphan concentration ($\rho = 0.225$) with pupillary diameter change (fig. 5B). This discrepancy may be caused by contradictory actions of dextromethorphan and dextrorphan. While mydriasis could be exerted by the noradrenergic or α agonist activities of dextromethorphan, miosis is believed to rather be mediated by dextrorphan. Therefore, the pupillary diameter change cannot be attributed solely to plasma concentrations of either of these compounds, but appears to be a result of their combined effects. According to Slanar *et al.*,[47] we may hypothesize that there is a potential cutpoint of metabolic ratio discriminating whether or not a significant mydriatic reaction occurs after dextromethorphan intake. This needs to be confirmed by measuring the effect of each drug—dextromethorphan and dextrorphan—alone and in combination, on pupil diameter and sedation.

Concerning cognitive parameters, reaction time (fig. 4) but not movement time was impaired by dextromethorphan, suggesting that dextromethorphan impaired the timing of decision and response programming processes but not motor preparation and motor response. The learning effect during the reaction time test, illustrated by a modest decrease of reaction time after each repeated test, was amplified with placebo compared to dextromethorphan ($P < 0.02$). Such a defect in learning with dextromethorphan could be explained by the impairment of learning and memorization mediated by antagonists of the NMDA receptor,[12] rather than by a sedative effect that was similarly little reported in both groups. This specific impact of dextromethorphan on new learning would benefit from exploration in future studies with other specific cognitive tests like Paired Associates Learning (Cambridge Neuropsychological Test Automated Battery). More specifically, it appears that it is dextrorphan that is associated with the increased reaction time ($P = 0.001$), a test that is related to cognitive function and may reflect cognitive impairment.[48] These findings concur with the current view that adverse effects of dextromethorphan would be related to its metabolite dextrorphan.[49]

This study has several limitations. First, the study was linked to the hyperalgesia model described by Kilo *et al.*[13] that was chosen because it was described to induce a 72-h stable hyperalgesia.[13,27] Assessment of this pain model stability in the placebo group showed, however, that secondary hyperalgesia was maintained after day 1 for only 10 out of 20 individuals (50%), limiting the assessment of the antihyperalgesic clinical effect with repeated dextromethorphan dosages because of the variability of the model itself. A second limitation is that this study may not be generalized to the general population due to the absence of females, non-Caucasians, and volunteers outside the 18- to 45-yr-old age range, and with a diversity of CYP450 profiles. In order to generalize our results, it would be interesting in the future to include patients suffering from pain with hyperalgesic characteristics of both sexes, all ages, and a stratification on the pharmacogenetics profile. A third

limitation is that this model is a surrogate of central pain sensitization, but not of neuropathic pain.

Collective data show that dextromethorphan is antihyperalgesic and that it reverses peripheral and central neuronal sensitization in the freeze-injury pain model. Results suggest that NMDA receptor must be sensitized by pain for dextromethorphan to be effective, as it showed no intrinsic antinociceptive effect in acute pain on healthy skin. The major item of information this study provided is the antihyperalgesic efficacy in humans of dextromethorphan at a low single dose of 30 mg, whereas previous studies mainly assessed this effect on animals or with higher dosage in humans (*e.g.*, 270 mg[7]; 960 mg/day[32]). The effects on pupillary diameter showed in humans that the antihyperalgesic effect of dextromethorphan is not accompanied by a sedative effect. It also underlined that dextromethorphan does not have opioid-like effect, a consideration often encountered in the literature. Finally, our results suggest that the main dextromethorphan metabolite, dextrorphan, may be responsible for deleterious cognitive impairment. Future trials with dextromethorphan combined with CYP450 modulators, inhibitors,[8,9] and inducers in patients suffering from hyperalgesia are required to confirm these new findings and provide a therapeutic option for vulnerable patients with refractory pain.

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## Competing Interests

The authors declare no competing interests.

## Reproducible Science

Full protocol available at: gisele.pickering@uca.fr. Raw data available at: gisele.pickering@uca.fr.

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