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ORIGINAL RESEARCH

Milnacipran poorly modulates pain in patients suffering from fibromyalgia: a randomized double-blind controlled study

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Introduction: Fibromyalgia is characterized by widespread and chronic pain, and its prevalence is increasing worldwide. Milnacipran, an antidepressant, is often prescribed for fibromyalgia with a possible beneficial effect on central pain modulation. The aim of this study was to evaluate if milnacipran could modify the status of conditioned pain modulation (CPM) in patients suffering from fibromyalgia.

Design and setting: Randomized, double-blind controlled trial.

Subjects and methods: Women with fibromyalgia received milnacipran 100 mg or placebo. The primary end point was the evolution of CPM with treatments after a 30-second painful stimulus. Secondary outcomes included the predictability of milnacipran efficacy from CPM performance, evolution of global pain, mechanical sensitivity, thermal pain threshold, mechanical allodynia, cognitive function, and tolerance.

Results: Fifty-four women with fibromyalgia (46.7±10.6 years) were included and randomized, and 24 patients were analyzed in each group. At inclusion, CPM was dysfunctional (CPM_{30}=–0.5±1.9), and global pain was 6.5±1.8. After treatment, there was a nonsignificant CPM difference between milnacipran and placebo (CPM_{30}=–0.46±1.22 vs –0.69±1.43, respectively, p=0.55) and 18.8% vs 6.3% (p=0.085) patients did reactivate CPM after milnacipran vs placebo. Initial CPM was not a predictor of milnacipran efficacy. Global pain, mechanical and thermal thresholds, allodynia, cognition, and tolerance were not significantly different between both groups.

Conclusion: Milnacipran did not display a significant analgesic effect after 1-month treatment, but the tendency of milnacipran to reactivate CPM in a number of patients must be explored with longer treatment duration in future studies and pleads for possible subtypes of fibromyalgia patients.

Keywords: fibromyalgia, CPM, milnacipran, antidepressants, pain

Introduction

Fibromyalgia (FM) is characterized by diffuse chronic pain affecting 0.5%–5% of the general population, with a female predominance.[1–4] Symptoms include joint and muscle pain associated with fatigue, migraine, sleep disorder, depression, and/or irritable bowel syndrome.[5–10] Symptom presentation varies greatly between individuals, with a wide variety of clinical, physical, social, and psychological repercussions and of therapeutic responses. Studies on FM pathophysiology report hyperalgesia to experimental stimuli,[10,11–14] central nervous system abnormalities and cerebral changes,[15–19] autonomic and neuroendocrine system abnormalities,[20] genetic factors,[21] and microbiota specificities.[22]

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Alteration in the central modulation of pain and diffuse noxious inhibitory controls has been demonstrated in FM patients[19,23–25] using an experimental psychophysics technique, conditioned pain modulation (CPM).[26–29] Dysfunction of neurotransmitters has also been described,[30–39] justifying the use of antidepressants in FM patients. Milnacipran inhibits the recapture of monoamines at presynaptic level,[40] with an increase in postsynaptic concentrations with CPM activation and diminution of pain.[41–43] Noradrenaline has a central analgesic action with a synergistic effect with serotonin,[41,44,45] and this would make milnacipran a good candidate for pain treatment. Milnacipran is recommended to treat FM in several countries, including North America and Russia.[46]

Duloxetine and milnacipran (both serotonin and norepinephrine reuptake inhibitor antidepressants) have shown a 30% reduction in pain, but in only 40% of the patients.[47–50]

Considering that CPM is poorly functional in FM patients,[51] the hypothesis is that milnacipran might reactivate the efficacy of pain modulation and restore the lost functionality of these central pathways. The present study aims to evaluate CPM efficacy with milnacipran compared to placebo after 1-month treatment.

Subjects and methods

Study design

This study is a prospective, randomized, controlled double-blind clinical trial with 2 parallel groups, milnacipran vs placebo in FM patients. It was carried out in the Pain Clinic/Clinical Pharmacology Center, University Hospital, Clermont-Ferrand, France, according to Good Clinical Practice. The Research Ethics Committee (CPP South East VI) gave its approval on October 18, 2012 (leading ethics committee number institutional review board [IRB] 00008526/AU987); the national Drug agency gave its approval on September 25, 2012 (EudraCT number 2012-003222-24); and this trial is registered in ClinicalTrials.gov (trial number NCT01747044).

Study population

At inclusion, written informed consent was obtained from all patients. Eligibility criteria were verified with a complete clinical examination matching the 2010 American College of Rheumatology definition of FM.[52] Patients were included if they fulfilled the following criteria: age >18 years with a confirmed diagnosis of FM, able to understand and follow the study protocol and have given informed consent. Patients were excluded if they met any of the following criteria: contraindication to milnacipran treatment, hypertension or heart disease, known renal impairment, patients with a medical and/or surgery history noncompatible with the study, and patients with a psychiatric disorder or with suicidal behavior/significant suicide ideas. This study also excluded patients with diabetes; patients taking alcohol, hypnotics, analgesics, and opioids; patients taking diuretics or a treatment inducing hyponatremia, nonsteroidal anti-inflammatory drugs, oral anticoagulants, aspirin, or other drugs that are likely to induce bleeding, drugs with serotonin and noradrenalin reuptake inhibition, digitalis, CYP1A2 inhibitors, and 5HT1D agonist. Also excluded were women of childbearing potential not using an effective contraceptive, pregnant or breastfeeding, taking part in another interventional trial or unable to understand patient information and informed consent form.

Study treatment

Patients were selected, included, and then randomized to oral milnacipran (IXEL®, batch number G00771, G00793, G00794) or oral placebo for 1-month treatment (Figure 1), with the following titration: 50 mg on the first 3 days, 75 mg from Day 4 to Day 6, and 100 mg from Day 7 to 1 month (M1), and the last treatment administration was on the evening before M1 visit where evaluations and tests, similar to inclusion, were carried out. The capsules of placebo were made and packaged by the pharmacy department (authorization number 2015-704) of the University Hospital of Clermont-Ferrand, France.

To maintain a good compliance and to verify adverse events (AEs), patients were called once a week by a clinical research assistant. Treatment allocation followed a predefined randomization plan and was conducted by a person independent from the protocol. The randomization sequence was generated using random blocks.

Objectives and study outcome variables

The primary objective of this trial was to assess if milnacipran has an influence on pain modulation profile by comparing CPM changes after a 30-second stimulus (CPM_{30}) in milnacipran and placebo groups. The secondary objectives were to 1) compare CPM changes after 10 seconds (CPM_{10}) in milnacipran and placebo groups, 2) assess the evolution of pain thresholds with milnacipran, 3) evaluate if CPM at inclusion could be predictive of milnacipran efficacy in FM, 4) explore the impact of milnacipran on cognitive parameters (comprehension tests, executive function, memory, attention, and decision making), and 5) evaluate the tolerance to milnacipran.

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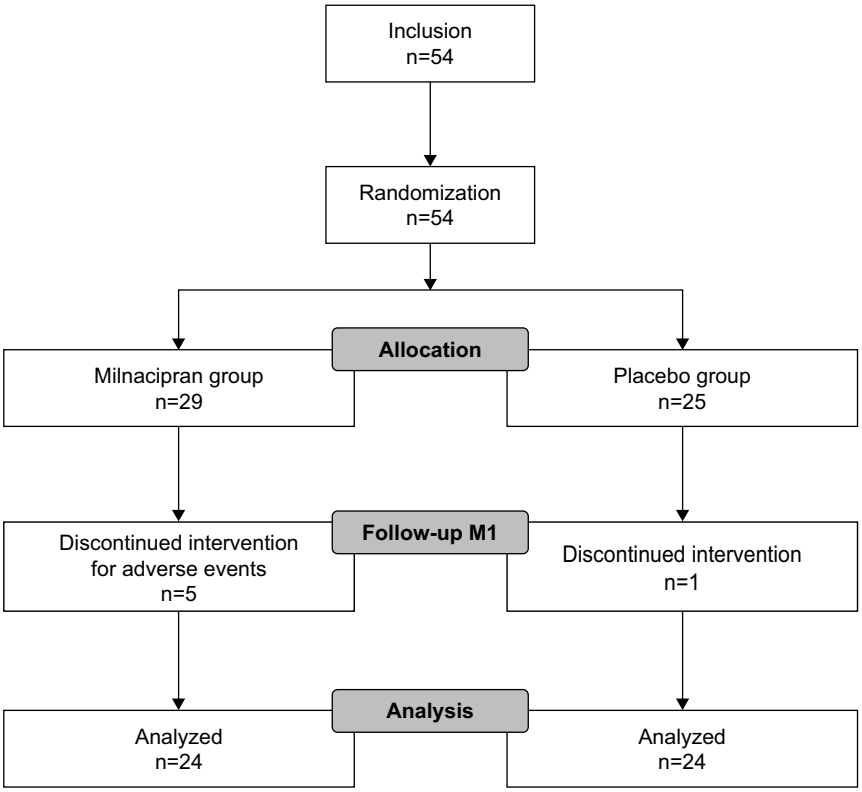


Figure 1 CONSORT study flow chart.

Outcome measures

Pain evaluation and pain responders

Pain intensity was measured by the Numeric Pain Rating Scale (NRS), and patients verbally rated the intensity of pain on a scale from "0" (no pain) to "10" (worst pain possible). "Pain responders" were patients presenting a 30% improvement in pain score at M1.

Assessment of pain thresholds to a thermal stimulus

The advanced thermal stimulation (ATS) thermode (30×30 mm) (Medoc Ltd., Ramat Yishai, Israel) connected to Pathway-Medoc® was applied to the volar side of the patient-dominant forearm. From the baseline value of 32°C, the Pathway-Medoc delivers an adjustable temperature peak (in cold and heat, depending on a regular slope of 1°C) and is controlled by rapid feedback. This device was used to evaluate the heat pain threshold (HPT) and cold pain threshold by calculating the mean of 3 measures. This technique has been used successfully in neurophysiology studies in humans[53] and showed similar results than those obtained with a laser.[54]

Test stimulus intensity "pain 60/stimulus"

The ATS thermode was applied to the volar side of the patient-dominant forearm. From the baseline value of 32°C, the Pathway-Medoc delivered a series of peaks starting from 1°C above HPT. Then the temperature was increased by 1°C until the patient rated the pain intensity equivalent to 6/10 on the NRS. The temperature (T6/10) corresponding to this 6/10 rated pain intensity was used for the CPM test.

Conditioned pain modulation

The ATS thermode was applied to the volar side of the patient-dominant forearm. The Pathway-Medoc delivered stimulation at the predetermined T6/10 for a duration of 10 seconds, and the patient rated her pain using the NRS. Then, the Pathway-Medoc delivered a stimulus at the same temperature for a duration of 30 seconds, and the patient rated her pain with NRS. After these stimuli (15 minutes), the patient put the nondominant hand for 60 seconds in a water bath at 46.5°C. After having dried her hand, the patient had another sequence of stimuli of 10 and 30 seconds with NRS pain evaluation. The aim of this test was to trigger the stimulation of inhibitory pain descending pathways. If these pathways were functional, the second series of stimuli would be less painful than the first series because of the inhibitory effect on pain as described in a number of chronic pain situations including FM.[53,55,56] CPM is calculated as the difference (for 10- and 30-second stimulation [CPM_{10} and CPM_{30}, respectively]) between the

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NRS pain scores rated after and before immersion of the nondominant hand in the water bath at 46.5°C. Delta CPM is the CPM difference between M1 and inclusion.

Pain modulation profile

Laboratory-based pain modulation using the CPM test as described previously allows to explore a pain modulation profile[57] based on the CPM response (<0, 0, or >0) and to classify patients on a scale with an "inhibitory" status (pain inhibition, CPM<0), a "facilitatory" status (pain facilitation, when patients have a CPM>0), and a "neutral" status (no inhibition or facilitation, with CPM=0).

Cantab® tests

The Cambridge Neuropsychological Test Automated Battery (Cantab, Cambridge, UK)[58] is a battery of 22 neuropsychological tests administered to subjects using a touch screen computer and a press-pad. The selected tests are as follows: spatial memory was evaluated with the Stockings of Cambridge test, a test of spatial planning and working memory; choice reaction time was an attention test, which measures the speed of response and movement in 5-choice paradigm; decision making and risk-taking outside a learning context with Cambridge Gambling Task, this test dissociates risk-taking from impulsivity; semantic memory was explored with the Graded Naming Test that gives a measure of semantic memory by assessing object-naming ability.

Mechanical allodynia

Mechanical allodynia was assessed by using a standardized brush (Somedic, Hörby, Sweden) with moving innocuous stimuli applied in a balanced manner on the volar side of the patient nondominant forearm, and the patient rated pain on a "0–10" NRS.

Mechanical sensitivity

Mechanical sensitivity was measured with a standardized set of modified von Frey® hair (Optihair2-Set; Marstock Nervtest, Schriesheim, Germany) that exert forces upon bending between 0.25 and 512 mN. von Frey hair was applied 3 times to the volar side of the patient nondominant forearm with increasing hair diameter until the patient felt 2 of the 3 stimuli. This hair diameter was considered as the mechanical sensitivity threshold.

Temporal summation

Temporal summation was realized using von Frey hair (180 g, size 6.45), applied to the volar side of the patient nondominant forearm. The 6.45 von Frey hair was applied once, and the patient rated her pain with NRS. The 6.45 von Frey hair was then applied 10 times at a rate of 1 Hz (1 stimuli per second), and the patient rated her pain. Temporal summation was calculated as the difference (for 1 and 10 stimuli) between the NRS pain scores.

Statistical analysis

According to our previous works and literature,[28] we estimated that a sample size of n=24 patients per randomized group would provide 90% statistical power to detect an absolute difference of 1.5 points (SD of CPM at 1.6) in the primary outcome. A 2-sided p-value of <0.05 was considered to indicate statistical significance for the change in CPM effect between milnacipran and placebo. Statistical analysis was conducted on per protocol analysis.

Baseline characteristics have been presented for each randomized group as the mean±SD or the median (interquartile range) according to statistical distribution for continuous data and as the number of patients and associated percentages for categorical parameters. Comparisons between independent groups have been analyzed using the chi-squared or Fisher's exact test for categorical variables and Student's t-test or Mann–Whitney test for quantitative parameters (notably primary outcome, temporal summation, test stimulus intensity pain 60/stimulus, pain rating on the NRS, cognitive parameters), with normality verified by the Shapiro–Wilk test and homoscedasticity by the Fisher–Snedecor test. As suggested by Vickers and Altman,[59] the primary analysis has been completed by analysis of covariance considering CPM at 1 month as a dependent variable[28] and group and baseline value of CPM as independent parameters. No missing data occurred in this work. Analyses were conducted using SAS9.4 for Windows (SAS, Cary, NC, USA).

Results

Patients and baseline characteristics

Fifty-four women with FM (46.7±10.6 years old) were included between April 2013 and December 2016 and 48 (per protocol analysis) were analyzed (Figure 1). FM duration was 91.3±86.0 months in the milnacipran group vs 52.4±33.3 months in the placebo group (p=0.048). Six patients (11%) discontinued the study, 5 patients (9%) in the milnacipran group for adverse events and 1 patient (2%) in the placebo group for personal reasons. Characteristics of the population at inclusion are indicated in Table S1. At inclusion, CPM was dysfunctional (CPM_{10}=–0.1±1.6, CPM_{30}=–0.5±1.9).

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Considering CPM_{30}, at baseline, global distribution of pain modulation profile was of 40% inhibitor, 29% facilitator, and 31% neutral. In the milnacipran group, 12.5% were inhibitor, 18.8% facilitator, and 18.8% neutral. In the placebo group, 27.1% were inhibitor, 10.4% facilitator, and 12.5% neutral (percentage of total number of subjects n=48). No significant difference in the distribution was observed (p=0.131).

Efficacy results

At M1, CPM_{30} was similar in milnacipran and placebo groups (–0.46±1.22 vs –0.69±1.43, respectively, p=0.552; Figure 2). Similarly, no difference was found for CPM_{10} (respectively for milnacipran and placebo groups, 0.0±1.44 vs –0.27±1.05, p=0.462). The differences between inclusion and M1 were also similar in milnacipran and placebo groups, both for CPM_{10} (0.06±1.98 vs –0.21±1.59, respectively, p=0.604) and CPM_{30} (–0.44±2.00 vs 0.35±2.1, respectively, p=0.188).

Regarding the evolution of pain modulation profile with treatment, 18.8% patients turned to an "inhibitory" profile in the milnacipran group and 6.3% in the placebo group (p=0.085; Figures 3 and 4).

Considering pain scores, no difference was observed between the milnacipran and placebo groups, either for raw values (5.3±2.5 vs 5.6±1.8, respectively, p=0.560) or for differences from baseline (–1.0±2.1 vs –1.0±1.7, respectively, p=0.971; Figure 5), whereas a significant reduction in pain scores was observed from baseline to M1 in both groups (p=0.029 and p=0.010). Regarding patients considered as "pain responders", 29% of patient reported a 30% improvement of pain in the milnacipran group vs 25% in the placebo group (p=0.745).

Thermal thresholds (cold and hot), mechanical allodynia, mechanical sensitivity threshold, temporal summation, and cognitive tests were not significantly different between both groups at M1 (Tables S2 and S3).

FM patients had cognitive impairment when compared with healthy volunteers of another study in our center (same age and sex) (Corriger et al, unpublished data, 2017).

Safety and compliance

Adverse events were reported by 45 patients (94% of included patients, 96% in the milnacipran group and 92% in the placebo group). These were mainly gastrointestinal disorders (28.4% vs 29.6%), general disorders (14.7% vs 18.5%), and nervous system disorders (14.7% vs 16.7%) (Figure 6). No serious adverse event was reported. Compliance to treatment

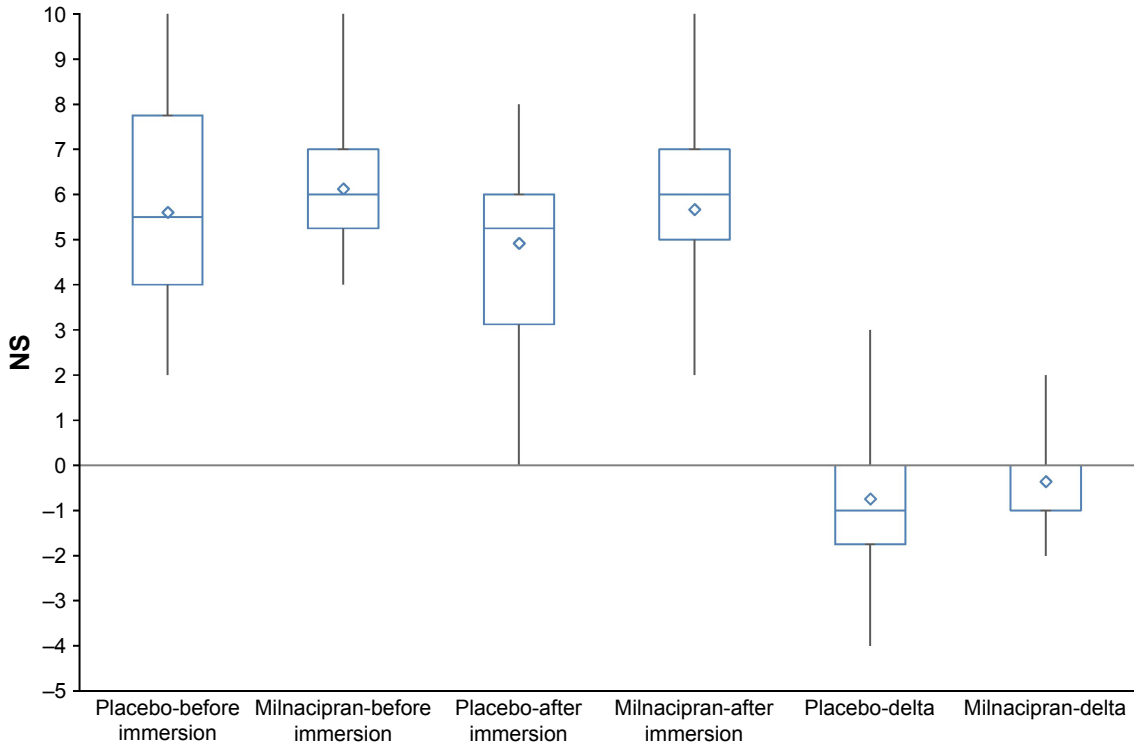


Figure 2 Pain evaluation (NRS) of 30-second conditioned pain modulation test at M1.
Abbreviation: NRS, Numeric Pain Rating Scale.

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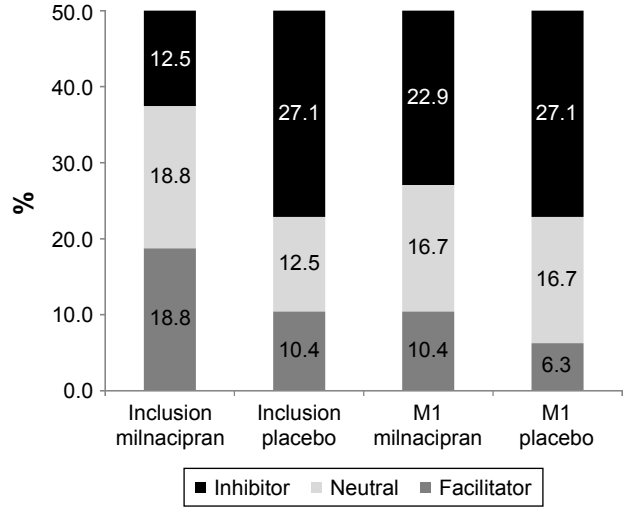


Figure 3 Percentage of patients according to the status of pain modulation profile (30-second conditioned pain modulation test) at inclusion and M1.

was 97.4% in the milnacipran group and 99.4% in the placebo group (p=0.41).

Discussion

This randomized double-blind controlled trial conducted in patients suffering from FM did not show any significant reactivation of CPM with milnacipran compared with placebo after a strong painful CPM stimulation. It is, however, interesting to note a trend (p=0.085) to develop an inhibitory profile after 1-month treatment with milnacipran, with more patients becoming "inhibitory" in the milnacipran vs placebo group (18.8% vs 6.3%, Figure 4). While 40% patients had an inhibitory status at baseline, 29% were facilitators (Figure 3), a figure higher than the 21.2% described in the study by Potvin and Marchand,[51] underlining the rather poor pain adaptation capability of FM patients. Similarly, no significant analgesic effect of milnacipran compared with placebo was observed on global pain, and pain diminished similarly in both groups, stressing the lack of efficacy of milnacipran and the strong placebo effect. This lack of analgesic effect is, however, contradictory to previous studies with milnacipran and duloxetine that showed[40–43,56] a pain diminution of 30% in 40% patients, a value higher than that in our study (30% diminution in 29% milnacipran group and 25% placebo group, p=0.745). The strong placebo effect observed in FM patients confirms, however, the literature on milnacipran[60] and was also shown for duloxetine and gabapentin. Patients in the placebo group had a shorter FM history duration than those in the milnacipran group. Kosek et al[61] reported that the shorter the duration of the history of FM, the stronger the placebo effect, suggesting a loss of placebo effect with time. Moreover, at baseline, while the dysfunction of CPM was obvious in both groups, a higher percentage of patients were classified as "inhibitor" in the placebo group (27.1% vs 12.5%). Despite adequate randomization, patients in the placebo and milnacipran groups displayed these slight differences that may have contributed to diminish the effect of milnacipran according to covariance analysis.

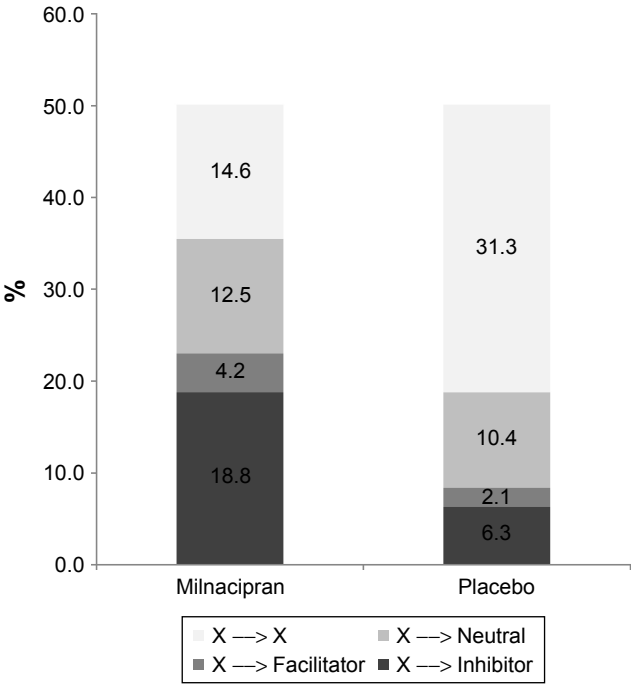


Figure 4 Pain modulation profile evolution (30-second conditioned pain modulation test) at M1.

Previous studies have shown that baseline pain modulation profile could be predictive of the efficacy of a treatment with duloxetine in patients with painful diabetic neuropathy.[28] Our study did not show any correlation between CPM at baseline and CPM after treatment or global pain after treatment. This point is consistent with the heterogeneity of responses to milnacipran in FM patients, suggesting that subtypes of FM may be at play, as suggested by Yim et al.[62] Knowledge of the pain modulation profile and characterization of FM subtype before treatment administration would allow to stratify patients to identify responders to milnacipran.

The study also investigated if cognitive function would be modified by milnacipran. Chronic pain and FM are known to have a deleterious influence on cognitivo-emotional domains, affecting emotion, concentration, and memory.[44,56,63] Our FM sample was cognitively impaired regarding vigilance and memory when compared with non-FM healthy volunteers from a previous study (Corriger et al, unpublished data, 2017).

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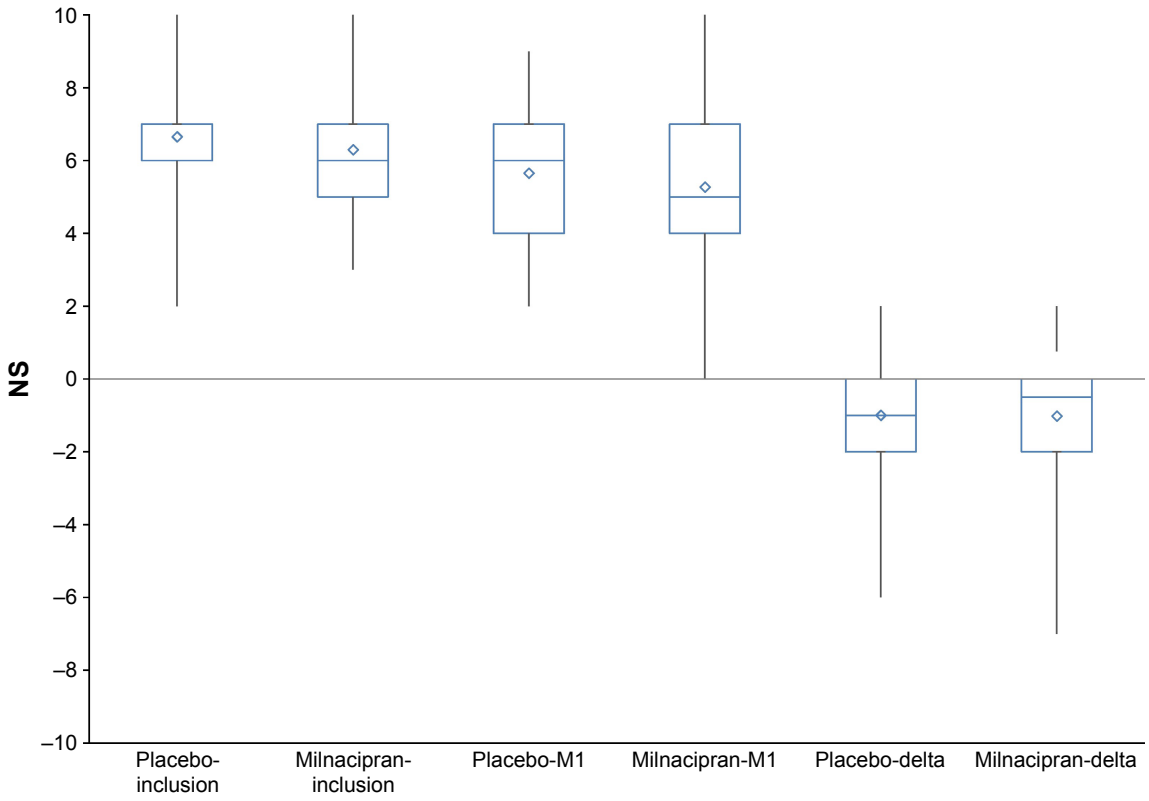


Figure 5 Global pain raw values (NRS) and differences at inclusion and M1.
Abbreviation: NRS, Numeric Pain Rating Scale.

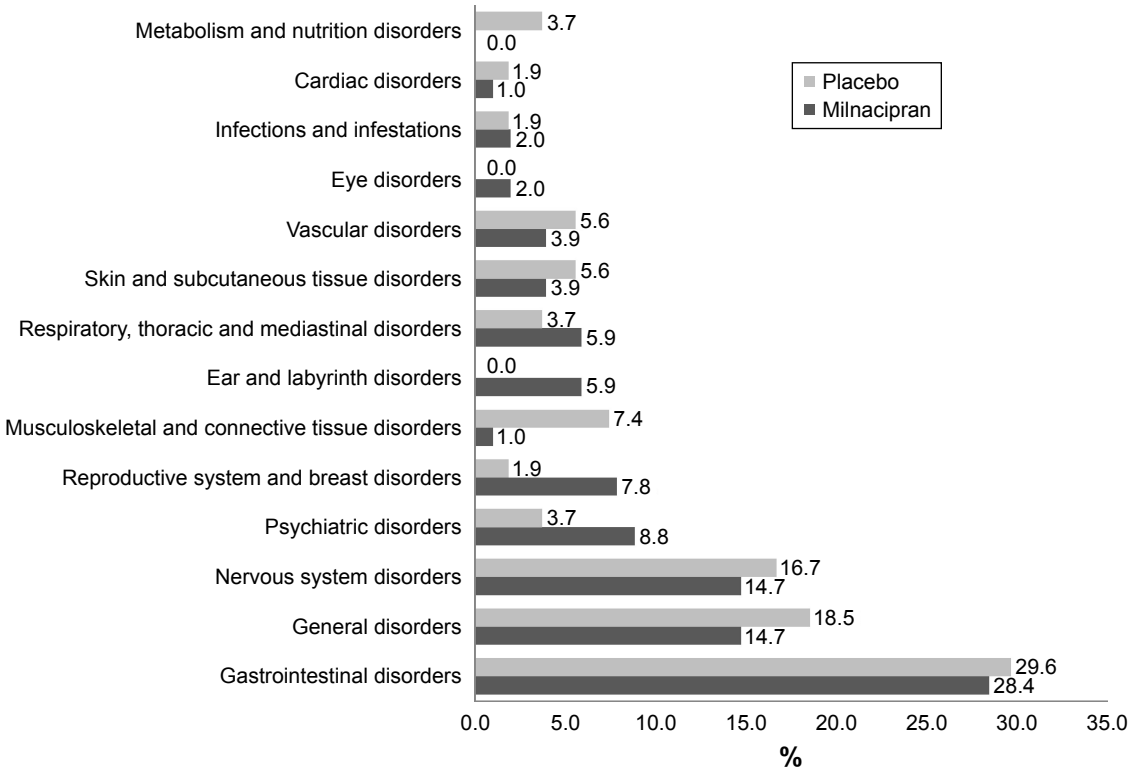


Figure 6 Reported adverse events.

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After 1-month treatment with milnacipran, no difference was, however, highlighted between both groups.

Finally, concerning tolerance, 96% FM patients developed serotonergic AEs in the milnacipran group as reported in the literature.[44,56,63] These AEs led to withdrawal from the protocol (5 patients in the milnacipran group, 1 in the placebo group), confirming data of a meta-analysis[45] that reported that milnacipran 100 mg daily was less well tolerated than duloxetine and pregabalin. However, FM patients with milnacipran reported AE described in the French drug label,[64] confirming the good compliance of patients to their treatment.

Limitations

Among limitations of our study, the length of the treatment was limited to 1 month, as milnacipran efficacy has been reported within 1–3 weeks treatment.[64] Another limitation concerns the fact that we included only women and no men in our experimental trial, in order to have a methodological homogeneity, although in real life the female:male ratio is 2:1.

Conclusion

A 1-month treatment with milnacipran did not show major reactivation of the functionality of CPM, and placebo and nocebo effects were observed. As milnacipran is recommended for FM in several countries,[65] it is important to stress the poor efficacy of milnacipran in the current trial, the occurrence of expected adverse events, and the large heterogeneity of FM patients concerning pain perception, pain modulation profile, and placebo effect. Stratification on CPM, inhibitory or facilitatory status, or FM history duration would allow to conclude on milnacipran pain alleviation in specific FM profiles. Larger clinical trials need to address these issues with multifactorial and multidimensional approaches to better subgroup FM patients to propose individualized therapeutic strategies.

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Author contributions

This clinical research was constructed by all authors. GP, FM, ND, PP, and BP conducted the study concept and design. GP, FM, ND, and PP preselected the patients suffering from fibromyalgia. GP and CD included the patients in the study. FG and NM realized the acquisition of data. GP, J-MC, CD, FM, BP, SS-A, and NM analyzed, interpreted, and wrote the first draft of the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper 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 Demographic and baseline characteristics of patient at inclusion

Parameter/test	Milnacipran, n=24	Placebo, n=24	*p*-value
FM duration (months), mean±SD	91.3±86.0	52.4±33.3	0.048
Age (years), mean±SD	48.0±11.0	44.3±9.3	0.210
Weight (kg), mean±SD	67.6±14.1	72.3±16.1	0.295
Treatment, n (%)	23 (95.8)	23 (95.8)	1.000
Global pain, numerical scale, NRS, mean±SD	6.3±2.0	6.6±1.6	0.501
Pain (CPM_{10}), before immersion, NRS, mean±SD	6.0±1.22	5.96±1.05	0.900
Pain (CPM_{10}), after immersion, NRS, mean±SD	5.9±1.9	5.9±1.2	0.927
CPM_{10}, mean±SD	−0.06±1.90	−0.06±1.34	1.000
Pain (CPM_{30}), before immersion 30 s, NRS, mean±SD	5.9±1.65	6.4±1.5	0.223
Pain (CPM_{30}), after immersion 30 s, NRS, mean±SD	5.8±2.3	5.4±2.5	0.506
CPM_{30}, mean±SD	−0.02±1.52	−1.04±2.15	0.065
Pain modulation profile			
Inhibitors, CPM_{10}, n (%)	7 (14.6)	10 (20.8)	
Facilitator, CPM_{10}, n (%)	8 (16.7)	8 (16.7)	0.589
Neutral, CPM_{10}, n (%)	9 (18.8)	6 (12.5)	
Inhibitors, CPM_{30}, n (%)	6 (12.5)	13 (27.1)	0.131
Facilitator, CPM_{30}, n (%)	9 (18.8)	5 (10.4)	
Neutral, CPM_{30}, n (%)	9 (18.8)	6 (12.5)	
Thermal heat pain sensitivity, °C, mean±SD	35.0±1.1	34.5±0.6	0.077
Thermal cold pain sensitivity, °C, mean±SD	29.9±0.9	29.9±1.3	0.942
Thermal heat pain threshold, °C, mean±SD	39.7±2.9	40.4±3.7	0.508
Thermal cold pain threshold, °C, mean±SD	24.5±5.0	24.2±5.5	0.846
Thermal heat pain threshold (T6/10), °C, mean±SD	41.9±4.0	41.4±4.2	0.765
Mechanical allodynia, NRS, mean±SD	0.8±1.2	0.8±2.0	0.912
Mechanical sensitivity, von Frey®, mean±SD	3.5±0.4	3.5±0.3	0.507
Mechanical temporal summation, von Frey, NRS, mean±SD	2.0±1.8	2.3±1.6	0.614

Abbreviations: CPM, conditioned pain modulation; CPM_{10}, CPM for 10 seconds stimulation; CPM_{30}, CPM for 30 seconds stimulation; FM, fibromyalgia; NRS, Numeric Pain Rating Scale.

Table S2 Cantab® baseline characteristics of fibromyalgia patient at inclusion

Test, mean±SD	n	Milnacipran	n	Placebo	*p*-value
SOC MITT	23	7,047.6±6,200.6	24	9,836.7±7,030.8	0.160
SOC MSTT		3,295.9±4,352.8		2,997.1±4,369.3	0.817
SOC PSMV		7.1±2.5		7.5±2.3	0.564
RTI FCRT	24	424.6±101.2	24	442.1±135.3	0.617
RTI FCMT		518.9±120.4		507.9±136.4	0.768
CGT QDM	23	0.85±0.14	24	0.82±0.17	0.465
CGT DT		2,734.3±893.3		2,952.2±1,003.2	0.435
CGT RT		0.47±0.18		0.45±0.14	0.715
CGT RA		0.58±0.83		0.76±0.79	0.427
CGT DA	23	0.42±0.25	24	0.34±0.21	0.258
CGT OPB		0.44±0.18		0.43±0.14	0.768
GNT TC	23	21.3±4.6	24	21.4±3.3	0.972
GNT TE		8.7±4.6		8.6±3.3	0.972
GNT PC		71.1±15.2		71.2±11.0	0.972

Abbreviations: CGT, Cambridge Gambling Task; DA, delay aversion; DT, deliberation time; FCMT, five-choice movement time; FCRT, five-choice reaction time; GNT, Graded Naming Test; MITT, mean initial thinking time; MSTT, mean subsequent thinking time; OPB, overall proportion bet; PC, percent correct; PSMV, problems solved in minimum moves; QDM, quality of decision making; RA, risk adjustment; RT, risk taking; RTI, reaction time; SOC, Stockings of Cambridge; TC, total correct; TE, total errors.

Table S3 Comparison between groups at M1

Test	n	Milnacipran	n	Placebo	*p*-value
Thermal heat pain sensitivity, °C, mean±SD	24	34.6±0.7	24	34.7±1.0	0.900
Thermal cold pain sensitivity, °C mean±SD		29.6±1.3		30.0±1.0	0.298
Thermal heat pain threshold, °C, mean±SD		39.7±3.2		40.5±3.7	0.438
Thermal cold pain threshold, °C, mean±SD		23.5±6.1		22.5±6.4	0.598
Mechanical sensitivity, mean±SD		3.48±0.46		3.48±0.39	0.680
Mechanical temporal summation, NRS, mean±SD		2.29±1.4		2.04±1.63	0.571
Thermal heat pain threshold (T6/10), °C, mean±SD		42.3±3.9		41.8±3.9	0.599
Mechanical allodynia, NRS, mean±SD		1.63±2.18		1.21±2.34	0.509
SOC MITT	23	6,155.2±6,657.1	24	5,758.1±4,508.9	0.404
SOC MSTT		1,608.6±1,818.1		1,395.7±1,340.1	0.726
SOC PSMV		7.9±2.0		8.4±1.8	0.422
RTI FCRT	23	430.4±303.6	24	416.5±98.9	0.946
RTI FCMT		517.9±105.8		495.6±127.0	0.527
CGT QDM	22	0.89±0.13	24	0.84±0.16	0.298
CGT DT	22	2,308.1±988.2	24	2,378.4±929.7	0.605
CGT RT		0.50±0.17		0.48±0.15	0.529
CGT RA		0.60±0.88		0.90±0.95	0.249
CGT DA		0.34±0.22		0.33±0.22	0.567
CGT OPB		0.47±0.16		0.45±0.15	0.560
GNT TC	23	23.1±5.0	24	23.2±3.7	0.960
GNT TE		6.9±5.0		6.8±3.7	0.960
GNT PC		77.1±16.5		77.2±12.4	0.959

Abbreviations: CGT, Cambridge Gambling Task; DA, delay aversion; DT, deliberation time; FCMT, five-choice movement time; FCRT, five-choice reaction time; GNT, Graded Naming Test; MITT, mean initial thinking time; MSTT, mean subsequent thinking time; NRS, Numeric Pain Rating Scale; OPB, overall proportion bet; PC, percent correct; PSMV, problems solved in minimum moves; QDM, quality of decision making; RA, risk adjustment; RT, risk taking; RTI, reaction time; SOC, Stockings of Cambridge; TC, total correct; TE, total errors.

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