

Randomized Trial

Dual Reuptake Inhibitor Milnacipran and Spinal Pain Pathways in Fibromyalgia Patients: A Randomized, Double-Blind, Placebo-Controlled Trial

Alain Matthey, MD¹, Christine Cedraschi, PhD^{1,2,3}, Valerie Piguët, MD¹, Marie Besson, MD¹, Jocelyne Chabert, PhD¹, Youssef Daali, PharmD, Delphine Courvoisier, PhD⁴, Agnes Montagne, MD⁵, Pierre Dayer, MD¹, and Jules Desmeules, MD¹

From: ¹Division of Clinical Pharmacology & Toxicology, Multidisciplinary Pain Centre, Geneva University Hospitals, Switzerland; ²Division of General Medical Rehabilitation, Geneva University Hospitals, Switzerland; ³University of Geneva, Switzerland; ⁴Division of Clinical Epidemiology, University Hospital of Geneva, Switzerland; and ⁵CRD, Pierre Fabre Médicament, Boulogne Billancourt, France

Address Correspondence: Jules A. Desmeules, MD
Geneva University Hospitals
Division of Clinical Pharmacology & Toxicology
Multidisciplinary Pain Center
Gabrielle Perret-Gentil 4
1211 Geneva 14, Switzerland
E-mail: jules.desmeules@hcuge.ch

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association, (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might post a conflict of interest in connection with the submitted manuscript. This trial was supported by a grant from Pierre Fabre Médicament.

Manuscript received: 03-22-2013
Accepted for publication: 05-02-2013

Free full manuscript: www.painphysicianjournal.com

Background: Investigations based on quantitative sensory testing have consistently shown evidence of allodynia in fibromyalgia syndrome (FMS) patients involving both the spinal and supraspinal pain regulatory systems. Functional imaging studies have demonstrated enhanced neural activities in pain-related brain areas as well as impairment of pain inhibition in the descending nociceptive regulatory system. A higher state of excitability of spinal nociceptive neurons as evidenced by lowered nociceptive flexion reflex R-III (NFR) threshold was reported for FMS patients. The NFR procedure has been shown to be a valuable tool to evaluate pharmacologically active therapeutic agents at the spinal level.

Objective: Serotonin-noradrenaline reuptake inhibitors have been shown to reduce pain in FMS patients possibly through descending monoaminergic pain pathways modulation. This randomized double-blind placebo-controlled trial assessed the pharmacodynamic activity of the dual-reuptake inhibitor milnacipran (MLN) at the spinal level by means of the objective spinal NFR.

Study Design: Randomized, double-blind, placebo-controlled trial

Setting: A single academic medical center, outpatient setting

Methods: Seven-week exposure (100, 150, 200mg/day) in women fibromyalgia patients. Evaluation consisted of extensive quantitative sensory testing including determination of the NFR threshold, self-reported standard questionnaires investigating pain, visual analog scales, fibromyalgia impact, health-related quality of life, depression and anxiety questionnaires, as well as the Patient's Global Impression of Change (PGIC). Analysis of covariance adjusted for baseline value was used for all endpoints.

Results: Seventy-seven (39 placebo, 38 milnacipran all doses) out of 80 randomized patients were available for analysis. The absence of influence of MLN (any dose) on the NFR surprisingly contrasted with the dose-dependent analgesic effect observed in MLN-treated patients with an adjusted change difference of -18.4mm (-30.9; -5.8) in pain reduction between placebo and the maximum dosage (200 mg) MLN groups ($P = 0.02$). Unchanged depression and anxiety scores confirmed the predominant selectivity of the analgesic effect of MLN on nociceptive pain pathway. Self-reported questionnaires consistently reflected the positive effects of MLN on quality of life and psychological well-being. Odds ratio 5.1 for PGIC responders (i.e. much/very much improved) was significantly in favor of MLN ($P = 0.04$).

Conclusion: Milnacipran has a predominantly supraspinal analgesic effect as evidenced by the significant clinical benefits and the absence of changes in the nociceptive spinal reflex threshold. Higher dose was associated with higher pain reduction. Reported analgesia was independent of patients' emotional status.

Key words: Fibromyalgia; chronic pain, spinal nociceptive flexion reflex, milnacipran, dual-reuptake inhibitor, 5-HT noradrenaline re-uptake inhibitor, descending noxious inhibitory controls, quantitative sensory testing, Patient Global Impression of Change, Fibromyalgia Impact Questionnaires

Pain Physician 2013; 16:E553-E562

Fibromyalgia syndrome (FMS) is a complex chronic widespread pain disorder in which dysfunction of nociception is associated with cognitive trouble, sleep disturbances, and psychological distress. FMS has been clearly linked to altered central nervous system processing of nociceptive stimuli (1). Investigations based on quantitative sensory testing have consistently shown evidence of allodynia in FMS patients (2-5) involving both the spinal and supraspinal pain regulatory systems (6-8). Functional imaging studies have demonstrated enhanced neural activities in pain-related brain areas as well as impairment of pain inhibition in the descending nociceptive regulatory system (9,10).

Significant progress has been made in the understanding of the physiopathology of FMS. These advances, however, have not yet been translated into novel therapeutic solutions, and everyday pain management of FMS remains a considerable challenge often necessitating individually tailored and integrated approaches (1,11,12). In addition, FMS is associated with a high rate of disability and increased health care utilization in a proportion comparable to rheumatoid arthritis (13). Recently drugs capable of modulating the monoaminergic system have been regarded as a highly appropriate choice for the treatment of FMS patients. Milnacipran (MLN) is a dual serotonin-noradrenaline reuptake inhibitor (SNRI). MLN has been shown to be effective in reducing pain and improving quality of life in FMS patients (14-18) and has now been granted approval by the Food and Drug Administration (FDA) for this indication. Nevertheless, exact knowledge of the potential targets at various levels of the pain pathways that SNRIs are able to modulate is still incomplete.

A higher state of excitability of spinal nociceptive neurons as evidenced by a lowered nociceptive flexion reflex R-III (NFR) threshold was reported for FMS patients (4,19). The NFR procedure has been shown to be a valuable tool to evaluate pharmacologically active therapeutic agents at the spinal level (20). This phase II, placebo-controlled mechanistic study explored for the first time the effect of MLN on modulatory pain pathways and, more specifically, whether its central antinociceptive properties affect the NFR in FMS patients. In addition, the clinical benefit of a 7-week treatment regimen with MLN was assessed with global improvement and pain rating scales as well as functional and health-related questionnaires.

METHODS

Overview

This trial was designed according to the CONSORT statement and registered within ClinicalTrials.gov (NCT00757679). The protocol was approved by the local ethical committee in Geneva. FMS outpatients were either referred by rheumatologists or general practitioners. All patients provided written informed consent. Potential confounding endocrine and inflammatory etiologies were systematically excluded at screening.

Entry Criteria: Women patients over 18 years old who met the American College of Rheumatology (ACR) FMS criteria (21) were included if the following criteria were met: signed informed consent, negative urine pregnancy test at screening and use of adequate contraception or absence of childbearing potential, willingness to withdraw from CNS-active therapies, willingness to discontinue treatment with trigger point injections and anesthetics, and reported baseline weekly recall pain over 40 on a 0 – 100 mm visual analog scale (VAS).

Exclusion criteria: severe psychiatric illness, current major depressive episode or screening Beck Depression Inventory (BDI) > 25, history of substance abuse, epilepsy, active cardiac disease, severe chronic obstructive pulmonary disease, active liver disease, renal impairment, documented autoimmune disease, current systemic infection, active cancer, active peptic ulcer or inflammatory bowel disease (irritable bowel syndrome excepted), unstable endocrine disorder, pregnancy or breastfeeding, concomitant use of psychotropic drugs (including antidepressants or phytotherapy), sympathicomimetics, long-acting benzodiazepines, anticoagulants, antiepileptic drugs, centrally-acting muscle relaxants, Opioids, smoking (> 25 cigarettes a day).

Study Design

Overall Plan

This phase II clinical trial was conducted as an 8-week, single-center, double-blind, placebo-controlled, 2-parallel arms, randomized trial in female FMS outpatients. Following a screening visit (V1), patients entered a 1- to 4-week treatment wash-out phase. If eligible, patients were randomized (block size of 4 and 1:1 allocation ratio) at visit 2 (Day 1) into the MLN or placebo (PBO) group. A randomization list was computer-generated by the sponsor and allocation of treatments was done by the investigator accord-

ing to the chronological order of the occurring visit 2 (randomization visit). Once allocated to a subject, the treatment number remained the same throughout the study period. Access to sealed decoding envelopes was restricted to the sponsor study manager and the onsite investigator and pharmacist.

Once randomized, patients started a 3-week dose escalation period with a stepwise daily dose increase from 25 mg (q.d.) to 100, 150, or 200 mg/day (b.i.d. administration) according to tolerance. At visit 4 patients entered the fixed dose period. At week 7 (visit 5), or at the occurrence of a premature withdrawal (PW), primary and secondary criteria were assessed. Finally a down-titration period (3 to 9 days, depending on the eligible fixed dose) led to patients' study termination.

Outcome Measures

Primary Endpoint Objective Pain Threshold

The NFR is considered a specific and objective physiologic correlate of pain sensation (22- 24). The NFR was considered to be present (positive response) when an electromyographic response signal recorded at the patient's biceps femoris with a surface electrode appeared within a specific time window (90 – 300 ms) following a single short duration (0.5 ms) electric impulse delivered at the ipsilateral distal sural nerve. A more detailed description of the procedure can be found elsewhere (4). This procedure was recommended as a tool to evaluate the excitability state of spinal neurons in the assessment of neuropathic pain (25).

Secondary Endpoints

Secondary outcomes were recorded at baseline (V2) and either at the end of the fixed dose period (V5) or within the fixed dose period in case of PW according to the last observation carried forward (LOCF) imputation method.

Diffuse Noxious Inhibitory Control

Diffuse noxious inhibitory control (DNIC) activity was determined by comparing 2 NFR signals (AUC) elicited by identical electrical suprathreshold stimulations. The first NFR signal was recorded according to the basic procedure while, during the second recording, a tonic nociceptive stimulation (cold pressor rest, see below) was simultaneously applied to the patient's hand. The DNIC was expressed as the percent decrease between the 2 NFR amplitudes (AUC). A positive response was defined as a reduction of more

than 20%. DNIC restoration occurred when, in the same patient, a negative response at baseline turned positive at week 7 (26-28).

Quantitative Sensory Testing at the Periphery, Thermal Thresholds and Cold Pressor Tests

Thermal thresholds were measured by means of a thermal sensory analyzer (Medoc Advanced Medical Systems, Ramat-Yishai, Israel). The thermal sensory analyzer operates by a microcomputer-driven 9 cm² Peltier contact thermode. The stimulation surface was heated and cooled within a range of 0°C to 50°C. For each sequence and for both hot and cold, the linear rate of change was set at 1°C/second, with a baseline temperature of 32°C (29,30). The cold threshold was systematically used as a first evaluation. Perception and pain thresholds were assessed according to the method of limits (arithmetic mean from 4 measurements) (4).

The cold pressor test was used to assess pain tolerance to tonic intense pain stimulation. The device consisted of a water-filled container divided by a mesh screen; ice was kept on one side while the patient's hand was immersed in the other compartment. Water temperature was kept below 1.0°C in order to stimulate C fibers. A stirring device circulated the water and a thermosistor monitored the temperature. Subjects were instructed to only withdraw their hand when the provoked pain was "at the maximum bearable." A cut-off time of 2 minutes was set to prevent any tissue lesion. The maximum time and intensity of pain (Visual Analog Scale) at withdrawal were recorded (31,32).

Pressure Pain Thresholds

Each pressure pain threshold (PPT) (33) was assessed according to ACR 1990 criteria using a hand-held Somedic Sales AB pressure algometer (1 cm², 30 kPa/s, range 0 – 400 kPa). The assessment was performed bilaterally on the trapezius, epicondyle, trochanter, and knee (8 points). The derived criterion analysed was the overall PPT (mean of 8 PPTs).

Pain Scales

Average pain intensity was measured using 2 0 – 100 mm VASs (34): current pain VAS (average pain in the last 24 hours) and weekly-recall pain VAS (average pain over the previous week). Weekly-recall and current pain VAS scores were recorded at each visit (V1, V2, V3, V4, V5/PW). The regional pain score (RPS) assessed pain intensity in 21 areas of the body represented on a hu-

man chart. Intensity level could range from 0 (no pain) to 5 (intolerable pain) in each corresponding sketch (maximum score 105).

Psychological and Functional Assessments

French validated versions of the Fibromyalgia Impact Questionnaire (FIQ), the Short-Form Health Survey (SF-36), and the Psychological General Well-Being Index (PGWB) were used to assess the repercussion of the disease on quality of life (35-43). French validated versions of the Beck Depression Inventory-II (BDI), the State-Trait Anxiety Inventory (STAI-S-T), and the Coping Strategies Questionnaire (CSQ) were used to identify mood disorders. BDI and STAI-T, which reflects anxiety as a trait (stable emotional component) as compared to the present state of anxiety (STAI-S), were also recorded at screening. Fatigue and quality of sleep were assessed with the Multidimensional Fatigue Inventory (MFI) and the Medical Outcome Study-sleep Indexes (MOS).

Overall Impression of Change

The fibromyalgia-specific Patient Global Impression of Change (PGIC) (44,45) was used. Patients were asked to answer the question: "Since the start of the study, overall, your fibromyalgia is..." with a 7-point scale ranging from one "very much improved" to 7 "very much worse." The Physician Global Impression of change (PGI) assessing the investigator's perspective (7 points scale ranging from one "very much improved" to 7 "very much worse") and the Physician Global Rating score (PGR) answering the question: "What is your overall clinical impression for this patient" (one = best rating to 5) were used. PGIC and PGI were only recorded at V5.

Pharmacokinetic Analysis

Milnacipran was quantified after on-line extraction (microturbulent flow) coupled to liquid chromatography-tandem mass spectrometry detection (the limit of quantification was 0.5 ng/mL) (46).

Statistical Analyses

The statistical analyses of the study sample counting and standard description at baseline as well as those for the safety evaluation were performed by the sponsor using the SAS software for Windows, version 8.02 and at the investigating centers using the R software (2009 version, from the R Foundation for Statistical Computing, Vienna, Austria). The statistical analyses for the efficacy evaluation were performed at the investigating

centers using the R software. All statistical tests were 2-sided with a level of significance set at 0.05.

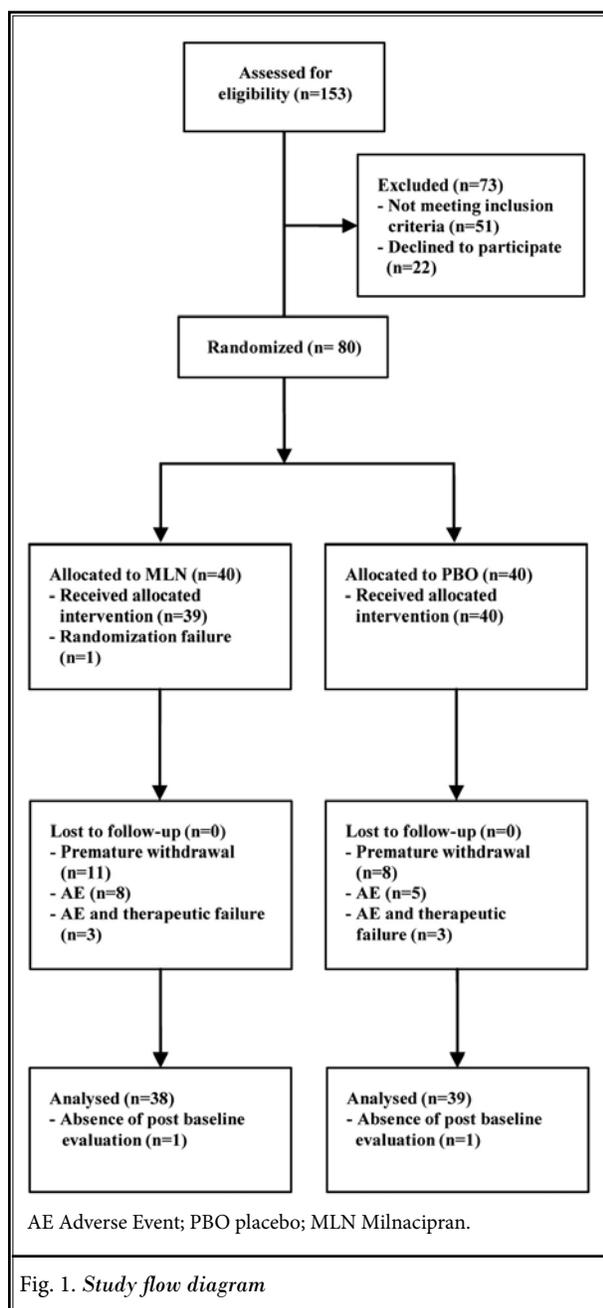
Sample size was calculated based on an expected difference of at least 6 mA (SD 9 mA) between the MLN and PBO groups on the change from baseline to the end of the fixed dose period on the NFR threshold (primary objective). Seventy-four patients were required to achieve an alpha of 0.05 and a power of 80%. Assuming that 7% of the patients would be excluded from the analysis, 80 patients were randomized. All randomized patients who received at least one dose of the randomized study treatment and had at least one evaluation criterion at V5 or PW were included in the analysis. A per protocol data set (PP) was used for supportive analysis on the primary efficacy criterion. The pharmacokinetic data set (PK) included data of all subjects receiving active treatment and for whom MLN concentration, with appropriate time and dosing records, were available.

The primary analysis was performed by imputing to missing data the last observation available. Analysis of covariance (ANCOVA) with baseline NFR value as covariate and treatment as main effect was used (adjusted model). Only patients with a post-baseline evaluation of the NFR were included in the NFR-derived criteria analyses. Since distributions of residuals were normal (based on visual inspection of residual vs. fit and QQ plots), only parametric methods were considered. Dose-related responses were examined for change in NFR and change in weekly-recall VAS pain scale by post hoc subgroups (tertiles) analyses of the MLN plasma concentration recorded at V5 and by subgroups of the maximal tolerated dose (100 – 150 mg, 200 mg). Odds ratio were calculated for changes in DNIC restoration, PGIC, and PGI variables using logistic regression comparing MLN group to PBO. Pearson's Chi-square test was used for the safety analysis.

RESULTS

Patient Disposition

A total of 153 FMS patients were screened, of whom 107 (69.9%) were selected following the screening visit. Eighty (52.3%), 40 in each group, were randomized. The data set included 38 patients in the MLN group and 39 in the PBO group. Fig. 1 presents the flow diagram of the trial. Socio-demographic and Disease Characteristics Patients socio-demographic and disease characteristics at baseline are reported in Table 1. The following symptoms were reported by more than 80% of the patients: fatigue (100%), morning stiffness



(96%), tingling in legs (89%), numbness in arms or legs (85%), and inability to concentrate (80%).

Study Drug Compliance

Compliance was assessed through the ratio of returned/taken capsules at each visit and overall. Treatment compliance reached similar proportions in both groups (88.6% overall).

Table 1. Patients' characteristics at baseline

	PBO (n=39)	MLN (n=38)
Age (y.)	50.9 (11.4)	48.5 (11.4)
BMI (kg/m ²)	26.6 (5.2)	25.1 (4.2)
Time from FMS diagnostic (y.)	6.0 (5.0)	5.0 (4.7)
Time from first FMS symptoms (y.)	10.5 (7.7)	12.1 (9.2)
Family history of FMS		
Yes	10 (26%)	16 (42%)
No	29 (74%)	22 (58%)
Number of tender points at screening	16.0 (2.0)	16.1 (1.4)
Objective NFR threshold at baseline (mA)	31.7 (14.2)	28.0 (15.8)
Weekly-recall pain VAS at baseline (mm)	62.1 (14.5)	63.7 (15.1)
Analgesic treatment at screening		
Antidepressants		
Yes	15 (39%)	17 (45%)
No	24 (61%)	21 (55%)
Other analgesics		
Yes	26 (67%)	27 (71%)
No	13 (33%)	11 (29%)
Benzodiazepine at screening		
Yes	10 (25%)	5 (13%)
No	29 (75%)	33 (87%)

BMI body mass index. PBO placebo; MLN Milnacipran

Efficacy Evaluation Objective

NFR Threshold

At week 7, the objective NFR threshold adjusted changes (SE) following electrical stimulation were similar in both groups: PBO + 5.5 mA (1.7) and MLN + 4.1 mA (1.8). Experimental Quantitative Sensory Testing DNIC test at baseline showed an overall low level of activity (median AUC decrease by 10.2%). Following 7 weeks of treatment, the activity remained unchanged in both groups.

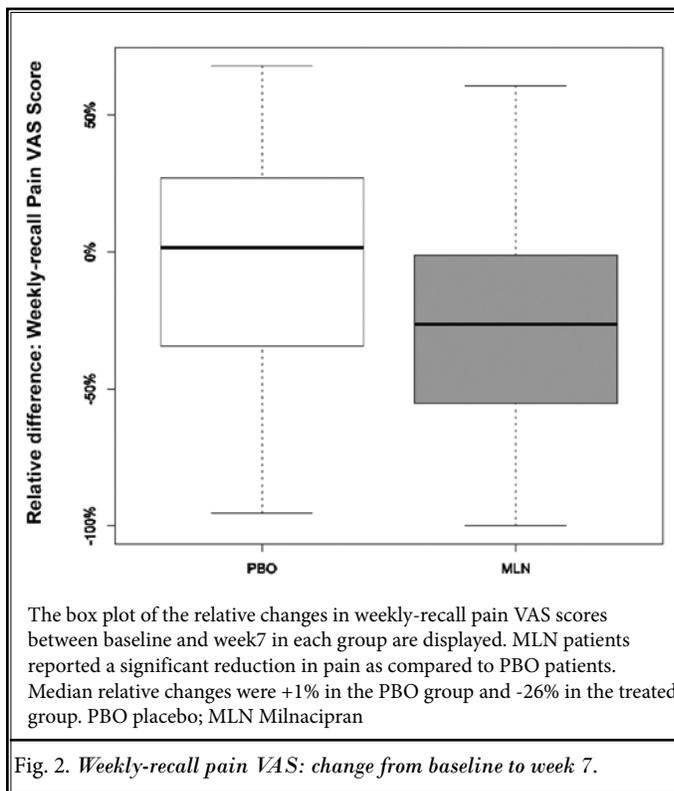
However, DNIC restoration was observed in 55% of patients who were on antidepressants at screening but only in 22% of patients who were not treated with psychotropic medications (OR 4.4, [95% CI: 1.2; 16.6], $P = 0.03$). Cold and heat allodynia were present in all FMS patients at baseline and remained unchanged at week 7. CPT and PPT were low at baseline, as expected, and were not influenced by treatment (Table 2).

Table 2. Quantitative sensory testing outcomes data.

	PBO		MLN		ACD	P-value	CI 95%
	Baseline	Week7	Baseline	Week7			
NFR Objective Pain Threshold (mA)	31.7 (14.2)	37.2 (19.4)	28.0 (15.8)	32.2 (16.1)	-1.4 (2.5)	0.58	[-6.3; 3.5]
DNIC (%)	18.4 (25.3)	24.4 (28.6)	26.3 (30.4)	24.9 (28.4)	-1.1 (7.1)	0.88	[-15.1 ; 12.9]
Cold Perception Threshold (°C):	30.3 (1.3)	30.3 (0.9)	30.3 (1.1)	30.0 (1.5)	-0.3 (0.3)	0.25	[-0.8 ; 0.2]
Warm Perception Threshold (°C):	34.2 (0.7)	34.4 (1.2)	34.3 (0.9)	34.3 (1.0)	-0.1 (0.2)	0.51	[-0.6 ; 0.3]
Cold Pain Threshold (°C)	21.0 (7.0)	20.2 (7.1)	21.0 (8.0)	20.5 (7.8)	0.5 (1.5)	0.76	[-2.5 ; 3.5]
Heat Pain Threshold (°C)	40.3 (4.3)	40.6 (3.9)	40.3 (3.9)	40.3 (3.4)	-0.4 (0.7)	0.56	[-1.8 ; 1.0]
CPT Tolerance Latency (s)	19.7 (14.5)	20.8 (15.3)	20.9 (28.2)	19.6 (26.5)	-2.0 (2.9)	0.49	[-7.6 ; 3.6]
CPT Pain VAS score (mm)	75.7 (15.0)	75.5 (15.0)	74.3 (13.6)	72.2 (16.6)	-2.6 (3.4)	0.45	[-9.2 ; 4.1]
PPT Overall (kPa/cm2)	187.1 (60.6)	188.9 (67.0)	182.8 (55.2)	180.4 (74.3)	-2.8 (11.0)	0.8	[-24.3 ; 18.8]

Baseline and week7 data are presented as mean (± SD) and the adjusted change difference (ACD) between groups as mean (± SE).

PBO placebo; MLN Milnacipran ; NFR nociceptive flexion reflex (0-100); DNIC diffuse noxious inhibitory control; CPT cold pressor test; PPT pressure pain Threshold. Mean values at baseline and week7 (end of treatment) and mean adjusted change differences between groups are displayed. MLN did not significantly modulate the activity of segmental spinal nociceptive neurons.



7 was -12.4 mm [-23.1; -1.6] ($P = 0.03$). Fig. 2 displays the relative changes in each group. The influence of the administered dose was further investigated and data suggested a dose-response relationship; the adjusted change difference [95% CI] in pain reduction (VAS) between MLN 200 mg and PBO groups was -18.4 mm [-30.9; -5.8] ($P = 0.02$). When plasma concentration of MLN was considered (tertiles of Cmin concentration at week 7), data indicated a concentration-response relationship; the adjusted change difference [95% CI] between PBO and the tertile with the highest plasma level of MLN was -34.2mm [-56.3; -12.2] ($P = 0.03$). Fig. 3 displays the relative changes in pain score for each MLN plasma concentration tertile and PBO. The regional pain score also showed a statistically significant adjusted change difference between groups in favor of MLN. While current VAS pain score change was not significantly different between groups, the direction of the effect was similar to the findings of weekly-recall VAS pain and RPS.

Health-related quality of life and function scores improved in the MLN group in comparison to the PBO group. Fatigue and quality of sleep were not influenced by treatment. None of the participants experienced at baseline a current depressive episode (exclusion criteria). CSQ scores in both groups at baseline indicated low levels of catastrophizing in the study population. BDI and STAI-S scores remained unchanged from baseline

Subjective Spontaneous Pain Scores at Week 7

MLN patients reported a significant reduction in pain on the weekly-recall pain VAS score as compared to PBO patients. The adjusted change difference [95% CI] between baseline and Week

Table 3. Quality of life and functional questionnaires outcomes data.

	PBO		MLN		ACD	P- Value	CI 95%
	Baseline	Week7	Baseline	Week7			
WRP VAS (mm)	62.1 (14.5)	58.3 (24.6)	63.7 (15.1)	46.7 (26.3)	-12.4 (5.5)	0.03	[-23.1 ; -1.6]
CP VAS (mm)	50.8 (21.8)	48.3 (25.1)	46.8 (18.7)	39.6 (23.1)	-6.0 (4.8)	0.22	[-15.4 ; 3.5]
RPS	48.1 (17.1)	49.8 (19.5)	44.2 (17.1)	38.6 (19.5)	-7.7 (3.3)	0.02	[-14.2 ; -1.3]
FIQ Total score	54.7 (14.4)	54.1 (18.6)	53.6 (17.0)	44.1 (20.8)	-9.1 (4.2)	0.04	[-17.4 ; -0.8]
SF-36 Physical Component	37.6 (6.9)	38.7 (7.3)	34.9 (7.5)	38.0 (7.7)	0.9 (1.4)	0.53	[-1.9 ; 3.7]
SF-36 Mental Component	38.4 (9.6)	36.0 (10.4)	41.0 (9.7)	45.0 (11.9)	7.3 (2.4)	<0.01	[2.6 ; 11.9]
PGWB Total index	50.6 (15.7)	48.7 (16.9)	53.7 (15.6)	59.4 (19.8)	8.3 (3.7)	0.03	[1.0 ; 15.5]
BDI -II Total score	12.6 (7.6)	15.0 (9.7)	10.6 (7.1)	10.8 (9.9)	-2.8 (1.9)	0.16	[-6.6 ; 1.1]
STAI (STAI-S)	39.6 (11.6)	49.1 (14.0)	38.3 (13.5)	38.7 (13.6)	-8.8 (2.7)	<0.01	[-14.0 ; -3.6]
CSQ Total score	12.9 (7.9)	13.0 (7.9)	12.7 (7.8)	10.2 (8.5)	-2.5 (1.5)	0.1	[-5.4 ; 0.4]
MFI Total score	66.9 (13.6)	66.2 (15.5)	65.7 (11.7)	61.0 (15.9)	-4.1 (2.8)	0.15	[-9.6 ; 1.4]
MOS-Sleep index I	58.5 (17.9)	52.9 (19.8)	57.1 (18.1)	52.3 (19.0)	1.1 (3.2)	0.74	[-5.2 ; 7.3]
MOS-Sleep index II	58.1 (17.7)	52.3 (20.3)	58.0 (18.1)	52.3 (18.0)	0.7 (3.1)	0.82	[-5.4 ; 6.8]

Baseline and week 7 data are presented as mean (\pm SD) and the adjusted change difference (ACD) between groups as mean (\pm SE).

PBO: placebo; MLN: Milnacipran; WRP: weekly-recall pain (0-100 worst); CP: current pain (0-100 worst); RPS: regional pain score (0-105 worst); FIQ: Fibromyalgia Impact Questionnaire (0-100 worst); SF: Short-Form Health Survey (0-100 best); PGWB: Patient General Well Being (0-110 best); BDI: Beck Depression Inventory (0-63 worst); STA: State-Trait Anxiety Inventory (20-80 worst); CSQ: Coping Strategy Questionnaire (0-36 worst); MFI: Multidimensional Fatigue Inventory (20-100 worst); MOS: Medical Outcome Study. Mean values at baseline and week7 (end of treatment) and mean adjusted change differences between groups are displayed.

in the MLN group. However, since PBO patients deteriorated on final evaluation, a between-group difference was observed for STAI-S. These scores remained unchanged at week 7 (Table 3). Scores from PGIC and PGI were congruent and demonstrated a clear benefit of MLN over PBO (OR = 5.1, [95% CI: 1.0; 25.9], $P = 0.04$), for PGIC responders (i.e. very much improved, much improved) and (OR = 2.3 [95% CI: 0.6; 8.6], $P = 0.20$) for PGI responders among patients in the MLN group as compared to the PBO. In addition, at week 7, PGR responder rate (i.e. 1, 2) was 59.4% in the MLN group as compared to 34.2% in the PBO group ($P = 0.04$).

Safety Evaluation

Thirty patients (81.1%) in the MLN and 36 (90%) in the PBO groups started the fixed dose period on the maximal dose (daily dose). Twenty-two (66.7%) in the MLN group and 32 (88.9%) in the PBO group ended the fixed dose period on the same daily dose.

As expected, with respect to MLN noradrenergic properties, vital sign time profiles showed an overall trend toward blood pressure and heart

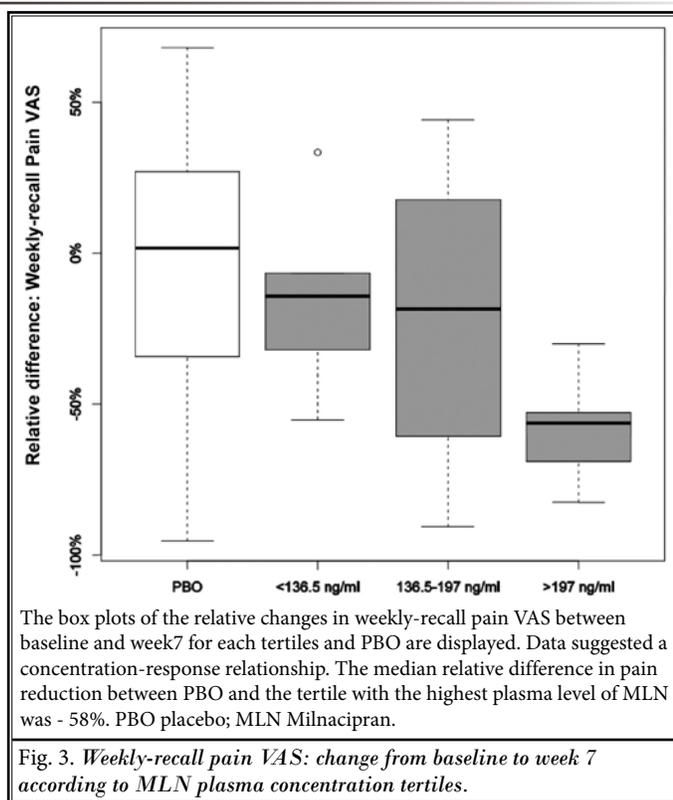


Fig. 3. Weekly-recall pain VAS: change from baseline to week 7 according to MLN plasma concentration tertiles.

rate increases in the MLN group at all doses. Ninety percent of MLN patients (vs. 38% in the PBO group) showed an increase of more than 10 mm Hg in either systolic or diastolic blood pressure ($P < 0.01$). Heart rate increased by more than 10 beats per minute was noted in 82% of the MLN patients vs. 28% in the PBO group ($P < 0.01$).

Shifts of individual status from normal to high blood pressure ($> 140/90$ mm Hg) were comparable between PBO and MLN-treated patients. Other adrenergic-related symptoms were reported with higher incidence by patients in the MLN group vs. PBO. These included hot flushes (49% vs. 18%, $P < 0.01$), hyperhidrosis (49% vs. 13%, $P < 0.01$), and constipation (41% vs. 15%, $P < 0.01$). There were no new safety signals.

Discussion

The analgesic effect of MLN was clearly demonstrated by the significant reduction on pain intensity scales and a higher proportion of responders (according to global evaluation scores (i.e. PGIC, PGI) in the MLN group. In addition, this group systematically reported improvement on quality of life and health-related questionnaires and post hoc pharmacokinetic analysis carried out on the most clinically relevant outcome (weekly-recall pain VAS) suggested an interesting dose- and plasma concentration-response relationships with MLN.

By contrast, the low magnitude of the adjusted change in the objective NFR threshold and the absence of group difference indicated that at these doses, MLN did not significantly modulate the activity of segmental spinal nociceptive neurons and treatment did not influence the DNIC activity or the documented thermoalgebra allodynia. In terms of safety profile noradrenergic-related adverse reactions were reported more often by the MLN treated population, as expected.

These results were quite unexpected since DNIC are essential components of the pain modulatory system that rely on spinal and supraspinal mechanisms through the release of noradrenalin and serotonin (47-49) and reduced DNIC activity has been linked to FMS (50,51). In parallel, modulation of thermal allodynia has been reported with SNRI in animal models (52,53). Therefore MLN was expected to modulate thermal allodynia and potentially restore normal DNIC activity. This absence of measurable effects of MLN on these different experimental pain modalities might have been related to the relatively low MLN dosage used in this study as compared to preclinical trials. Interestingly however, the DNIC restoration rate was significantly higher in

patients already taking antidepressants at screening regardless of the treatment group. This may suggest enhanced supraspinal inhibitory synaptic transmission capacity in patients treated with antidepressants.

The limitations of this study need to be considered when interpreting these results. We anticipated the possibility that the expected pain modulation might be related to the antidepressant properties of MLN. Patient selection based on BDI scores (under the cut-off for depression) was an essential step in neutralizing the influence of this potential key confounder.

Furthermore low scores on the STAI-S and the CSQ reflected the fact that the FMS patients included in this study, although chronically suffering from pain and allodynia, did not present any mood disorder. Moreover, the BDI score of MLN-treated patients remained unchanged throughout the study while mild deterioration was observed in the PBO group. Therefore these data suggest that the reported MLN analgesic effect was most likely unrelated to its antidepressant properties. Prior to randomization, patients had been asked to stop their usual analgesic treatment.

However, in order to address possible exacerbations of pain (FMS-related or headaches) during the course of the study that would be severe enough to require additional therapy, short-acting rescue analgesics and sedatives were allowed punctually under the control of the investigator, at the lowest possible doses and for the shortest periods of time. This flexibility was essential when taking into consideration the trial duration, the requirement of a washout period, and the potentially high rate of early withdrawal leading to selection bias. In order to prevent any interference with the study drug, analgesic prescriptions were carefully monitored and ample time (no less than 5 half-lives) was given before each evaluation visits (V2, V5) to ensure complete washout. Pharmacological treatment of FMS patients remains a difficult challenge particularly in the absence of a well defined causal factor that could be targeted by specific treatments. This study refines the pathophysiological mapping of FMS, better defines the site of action of MLN administered at the FDA-approved therapeutic dosage, and demonstrates that MLN-validated clinical benefits are clearly unrelated to its antidepressant properties.

Conclusion

Data suggest that MLN has a predominantly supraspinal analgesic effect as evidenced by the clear clinical benefits and the absence of changes in the nociceptive

spinal reflex. A higher dose was associated with higher pain reduction. The reported clinically significant benefit of MLN in reducing pain and improving quality of life was independent of patients' emotional status. The centrally acting analgesic properties of MLN could be related, at least partially, to the enhancement of inhibitory neurotransmission in cerebral pain modulatory pathways.

ACKNOWLEDGMENTS

We thank the patients for willingly giving their time to this study, the local research team for working very hard to complete this trial, and the Clinical Research Center (University Hospital and Faculty of Medicine, Geneva) for its contributions. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Matthey and Dr Desmeules had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: Cedraschi, Piguet, Besson, Chabert, Daali, Dayer, Desmeules.

Acquisition of data: Matthey, Cedraschi, Piguet, Besson, Chabert, Daali, Desmeules.

Analysis and interpretation of data: Matthey, Cedraschi, Courvoisier, Montagne, Desmeules.

Funding

Pierre Fabre Médicament (Boulogne Billancourt, France) provided funding. The study was designed by the investigators. Clinical data were collected by the investigators and entered into a Pierre Fabre Médicament database. Pierre Fabre Médicament statisticians and programmers ran the analyses on safety while the investigators conducted the efficacy analyses. The investigators prepared the manuscript. All authors and Pierre Fabre Médicament reviewed and approved the manuscript before submission and agreed to submit the final version.

REFERENCES

- Smith HS, Harris R, Clauw D. Fibromyalgia: An afferent processing disorder leading to a complex pain generalized syndrome. *Pain Physician* 2011; 14:E217-245.
- Smith BW, Tooley EM, Montague EQ, Robinson AE, Cosper CJ, Mullins PG. Habituation and sensitization to heat and cold pain in women with fibromyalgia and healthy controls. *Pain* 2008; 140:420-428.
- Staud R, Vierck CJ, Robinson ME, Price DD. Spatial summation of heat pain within and across dermatomes in fibromyalgia patients and pain-free subjects. *Pain* 2004; 111:342-350.
- Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum* 2003; 48:1420-1429.
- Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: Effects of stimulus type and mode of presentation. *Pain* 2003; 105:403-413.
- Burgmer M, Pogatzki-Zahn E, Gaubitz M, Wessoleck E, Heuft G, Pfeleiderer B. Altered brain activity during pain processing in fibromyalgia. *Neuroimage* 2009; 44:502-508.
- Staud R, Bovee CE, Robinson ME, Price DD. Cutaneous C-fiber pain abnormalities of fibromyalgia patients are specifically related to temporal summation. *Pain* 2008; 139:315-323.
- Staud R, Robinson ME, Price DD. Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *J Pain* 2007; 8:893-901.
- Jensen KB, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Giesecke T, Mainguy Y, Gracely R, Ingvar M. Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. *Pain* 2009; 144:95-100.
- Guedj E, Taieb D, Camilleri S, Lussato D, de Laforte C, Niboyet J, Mundler O. 99mTc-ECD brain perfusion SPECT in hyperalgesic fibromyalgia. *Eur J Nucl Med Mol Imaging* 2007; 34:130-134.
- Nijs J, Crombez G, Meeus M, Knoop H, Damme SV, Cauwenbergh V, Bleijenbergh G. Pain in patients with chronic fatigue syndrome: Time for specific pain treatment? *Pain Physician* 2012; 15:E677-686.
- Nijs J, Kosek E, Van Oosterwijck J, Meeus M. Dysfunctional endogenous analgesia during exercise in patients with chronic pain: To exercise or not to exercise? *Pain Physician* 2012; 15:ES205-213.
- Silverman S, Dukes EM, Johnston SS, Brandenburg NA, Sadosky A, Huse DM. The economic burden of fibromyalgia: Comparative analysis with rheumatoid arthritis. *Curr Med Res Opin* 2009; 25:829-840.
- Arnold LM, Gendreau RM, Palmer RH, Gendreau JF, Wang Y. Efficacy and safety of milnacipran 100 mg/day in patients with fibromyalgia: Results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2010; 62:2745-2756.
- Goldenberg DL, Clauw DJ, Palmer RH, Mease P, Chen W, Gendreau RM. Durability of therapeutic response to milnacipran treatment for fibromyalgia. Results of a randomized, double-blind, monotherapy 6-month extension study. *Pain Med* 2010; 11:180-194.
- Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W, Palmer RH. The efficacy and safety of milnacipran for treatment of fibromyalgia. A randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2009; 36:398-409.
- Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: A 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin Ther* 2008; 30:1988-2004.
- Branco JC, Zachrisson O, Perrot S, Mainguy Y. A European multicenter random-

- ized double-blind placebo-controlled monotherapy clinical trial of milnacipran in treatment of fibromyalgia. *J Rheumatol* 2010; 37:851-859.
19. Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, Curatolo M. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. *Pain* 2004; 107:7-15.
 20. Sandrini G, Serrao M, Rossi P, Romaniello A, Cruccu G, Willer JC. The lower limb flexion reflex in humans. *Prog Neurobiol* 2005; 77:353-395.
 21. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, G. Fam A, Farber SJ, Fiechtner JJ, Francklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33:160-172.
 22. Arendt-Nielsen L, Bennum J, Sindrup S, Bak P. Electrophysiological and psychophysical quantification of temporal summation in the human nociceptive system. *Eur J Appl Physiol Occup Physiol* 1994; 68:266-273.
 23. Willer JC. Nociceptive flexion reflexes as a tool for pain research in man. *Adv Neurol* 1983; 39:809-827.
 24. Willer JC, Le Bars D, De Broucker T. Diffuse noxious inhibitory controls in man: Involvement of an opioidergic link. *Eur J Pharmacol* 1990; 182:347-355.
 25. Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpaa M, Jorum E, Serra J, Jensen TS. EFNS guidelines on neuropathic pain assessment. *Eur J Neurol* 2004; 11:153-162.
 26. Bouhassira D, Le Bars D, Bolgert F, Laplane D, Willer JC. Diffuse noxious inhibitory controls in humans: A neurophysiological investigation of a patient with a form of Brown-Sequard syndrome. *Ann Neurol* 1993; 34:536-543.
 27. Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. *Pain* 1979; 6:305-327.
 28. Willer JC, Boureau F, Albe-Fessard D. Supraspinal influences on nociceptive flexion reflex and pain sensation in man. *Brain Res* 1979; 179:61-68.
 29. Claus D, Hilz MJ, Hummer I, Neundorfer B. Methods of measurement of thermal thresholds. *Acta Neurol Scand* 1987; 76:288-296.
 30. Jamal GA, Weir AI, Hansen S, Ballantyne JP. An improved automated method for the measurement of thermal thresholds. 2. Patients with peripheral neuropathy. *J Neurol Neurosurg Psychiatry* 1985; 48:361-366.
 31. Harris G, Rollman GB. The validity of experimental pain measures. *Pain* 1983; 17:369-376.
 32. Garcia de Jalon PD, Harrison FJ, Johnson KI, Kozma C, Schnelle K. A modified cold stimulation technique for the evaluation of analgesic activity in human volunteers. *Pain* 1985; 22:183-189.
 33. Petzke F, Khine A, Williams D, Groner K, Clauw DJ, Gracely RH. Dolorimetry performed at 3 paired tender points highly predicts overall tenderness. *J Rheumatol* 2001; 28:2568-2569.
 34. Lautenschlager J, Seglias J, Bruckle W, Muller W. Comparisons of spontaneous pain and tenderness in patients with primary fibromyalgia. *Clin Rheumatol* 1991; 10:168-173.
 35. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: Development and validation. *J Rheumatol* 1991; 18:728-733.
 36. Perneger TV, Lepage A, Etter JF, Rougemont A. Validation of a French-language version of the MOS 36-Item Short Form Health Survey (SF-36) in young healthy adults. *J Clin Epidemiol* 1995; 48:1051-1060.
 37. Finckh A, Morabia A, Deluze C, Vischer T. Validation of questionnaire-based response criteria of treatment efficacy in the fibromyalgia syndrome. *Arthritis Care Res* 1998; 11:116-123.
 38. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4:561-571.1970.
 39. Spielberger C D. State-Trait Anxiety Inventory. *Corsini Encyclopedia of Psychology*. Wiley Online Library 2010.
 40. Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic low back pain patients: Relationship to patient characteristics and current adjustment. *Pain* 1983; 17:33-44.
 41. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; 39:315-325.
 42. Stewart AL, Hays RD, Ware JE, Jr. The MOS short-form general health survey. Reliability and validity in a patient population. *Med Care* 1988; 26:724-735.
 43. Wenger NK, Mattson, M.E., Furbert C.D., Elison, J. Assessment of quality of life in clinical trials of cardiovascular therapies. *Am J Cardiol* 1984; 54:908-913.
 44. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94:149-158.
 45. Guy W. *Manual for Psychopharmacology*. 1976. https://openlibrary.org/books/OL24341821M/ECDEU_assessment_manual_for_psychopharmacology.
 46. Palmier C, Puozzo C, Lenehan T, Briley M. Monoamine uptake inhibition by plasma from healthy volunteers after single oral doses of the antidepressant milnacipran. *Eur J Clin Pharmacol* 1989; 37:235-238.
 47. Millan MJ. Descending control of pain. *Prog Neurobiol* 2002; 66:355-474.
 48. Stamford JA. Descending control of pain. *Br J Anaesth* 1995; 75:217-227.
 49. Chitour D, Dickenson AH, Le Bars D. Pharmacological evidence for the involvement of serotonergic mechanisms in diffuse noxious inhibitory controls (DNIC). *Brain Res* 1982; 236:329-337.
 50. Potvin S, Larouche A, Normand E, de Souza JB, Gaumond I, Grignon S, Marchand S. DRD₃ Ser9Gly polymorphism is related to thermal pain perception and modulation in chronic widespread pain patients and healthy controls. *J Pain* 2009; 10:969-975.
 51. Staud R, Robinson ME, Vierck CJ, Jr., Price DD. Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. *Pain* 2003; 101:167-174.
 52. Iyengar S, Webster, A.A, Hemrick-Luecke, S.K., Xu, J.Y., Simmons, R.M. Efficacy of duloxetine, a potent and balanced serotonin-norepinephrine reuptake inhibitor in persistent pain models in rats. *J Pharmacol Exp Ther* 2004; Nov:576-584.
 53. Jones CK, Eastwood BJ, Need AB, Shannon HE. Analgesic effects of serotonergic, noradrenergic or dual reuptake inhibitors in the carrageenan test in rats: Evidence for synergism between serotonergic and noradrenergic reuptake inhibition. *Neuropharmacology* 2006; 51:1172-1180.