

## Effect of Milnacipran Treatment on Ventricular Lactate in Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Trial

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**Abstract:** Milnacipran, a serotonin/norepinephrine reuptake inhibitor, has been approved by the US Food and Drug Administration for the treatment of fibromyalgia (FM). This report presents the results of a randomized, double-blind, placebo-controlled trial of milnacipran conducted to test the hypotheses that a) similar to patients with chronic fatigue syndrome, patients with FM have increased ventricular lactate levels at baseline; b) 8 weeks of treatment with milnacipran will lower ventricular lactate levels compared with baseline levels and with ventricular lactate levels after placebo; and c) treatment with milnacipran will improve attention and executive function in the Attention Network Test compared with placebo. In addition, we examined the results for potential associations between ventricular lactate and pain. Baseline ventricular lactate measured by proton magnetic resonance spectroscopic imaging was found to be higher in patients with FM than in healthy controls ( $F_{1,37} = 22.11$ ,  $P < .0001$ , partial  $\eta^2 = .37$ ). Milnacipran reduced pain in patients with FM relative to placebo but had no effect on cognitive processing. At the end of the study, ventricular lactate levels in the milnacipran-treated group had decreased significantly compared with baseline and after placebo ( $F_{1,18} = 8.18$ ,  $P = .01$ , partial  $\eta^2 = .31$ ). A significantly larger proportion of patients treated with milnacipran showed decreases in both ventricular lactate and pain than those treated with placebo ( $P = .03$ ). These results suggest that proton magnetic resonance spectroscopic imaging measurements of lactate may serve as a potential biomarker for a therapeutic response in FM and that milnacipran may act, at least in part, by targeting the brain response to glial activation and neuroinflammation. **Perspective:** Patients treated with milnacipran showed decreases in both pain and ventricular lactate levels compared with those treated with placebo, but, even after treatment, levels of ventricular lactate remained higher than in controls. The hypothesized mechanism for these decreases is via drug-induced reductions of a central inflammatory state.

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**M**ilnacipran, a serotonin-norepinephrine reuptake inhibitor (SNRI) and an antidepressant, has been approved by the US Food and Drug Administration for treatment of fibromyalgia (FM), a medically unexplained illness characterized by widespread pain with tenderness on palpation. However, the anatomical site(s) and mechanism of action of milnacipran in FM remain poorly defined. To advance understanding of the pharmacotherapy of milnacipran in FM, a randomized, double-blind, placebo-controlled trial of the drug was conducted with 2 major outcome variables.

The first targeted outcome variable was ventricular lactate level, which we hypothesized would be increased in FM because we previously reported the level of this metabolite to be increased in patients with chronic fatigue syndrome (CFS),<sup>15,17,21</sup> another medically unexplained illness that shares extensive symptom overlap and coexists with FM in at least 35% of patients.<sup>1</sup> To test the validity of this assumption, proton magnetic resonance spectroscopic imaging (<sup>1</sup>H MRSI) was used to measure ventricular lactate in patients with FM to determine whether its level was increased at baseline compared with normal controls, as was the case in CFS. Then, a double-blind, placebo-controlled trial was conducted to test the hypothesis that the effect of milnacipran treatment will be to lower and/or normalize ventricular lactate levels in patients with FM treated with the drug compared with FM patients treated with placebo and with normal controls.

The second outcome variable of interest in this study was cognitive processing speed on uncued and executive control latencies as assessed by the Attention Network Test (ANT),<sup>5</sup> a neuropsychological test that evaluates the person's aptitude in attention and information processing, which are adversely affected in patients with CFS and FM.<sup>23</sup> This outcome measure was used to test a secondary hypothesis, which was that milnacipran will improve cognitive performance in patients with FM who were treated with the drug compared with those treated with placebo.

## Methods

### Participants

Thirty-seven patients reporting the presence of widespread pain were brought to the Pain & Fatigue Study Center of Mount Sinai Beth Israel for evaluation; these patients were allowed to stay on their current medication regimen. A medical history corroborated the presence of widespread pain, defined as pain on both sides of the body, above and below the waist with an axial component, and a physical examination corroborated the presence of more than 10 of 18 tender points; points were counted as tender if patients reported them to be at least a 2 on a pain intensity visual analog scale (VAS) of 0 to 10.<sup>19</sup> The presence of both widespread pain and 11 or more tender points fulfilled the criteria for the diagnosis of FM.<sup>29</sup>

The total tenderness score for all enrolled patients was derived by summing the rating for each positive tender

point. Each participant was also asked to mark a 10-cm VAS (range: none to worst pain possible) to quantify their pain at that particular moment. In addition, each participant was evaluated to determine the existence of comorbid CFS<sup>7</sup> or irritable bowel syndrome,<sup>3</sup> and whether their illness began suddenly or gradually. After verification of the diagnosis of FM, each patient provided informed written consent to participate in the study, which was approved by the Institutional Review Boards of both Mount Sinai Beth Israel and Weill Cornell Medical College. Next, the patients were randomized to either the drug or placebo condition to allow equal numbers in each group. Randomization was done by Forest Laboratories and transmitted to the Mount Sinai Beth Israel Pharmacy, which dispensed the drug or placebo according to the randomization list in sequential order. See Fig 1 for the CONSORT diagram.

The patients with FM took part in a telephone interview for psychiatric symptoms using the Structured Clinical Interview of DSM-IV (SCID).<sup>6</sup> They also completed the following self-report questionnaires: the Multidimensional Fatigue Inventory (MFI), a 20-item questionnaire<sup>22</sup> that provides data about general fatigue on a scale of 1 to 5 for each question, where 1 is "yes, that is true" and 5 is "no, that is not true"; the Multiple Ability Self-report Questionnaire (MASQ), a 38-item questionnaire that assesses perceived function in 5 cognitive domains<sup>20</sup> on a scale of 1 to 5 for each question, where 1 is "never" and 5 is "always"; and the Centers for Epidemiological Study-Depression (CES-D), a 20-item questionnaire that provides data about depressed mood in the last week on a scale of 0 to 3, where 0 is "rarely" and 3 is "most of the time", with a total score of 16 as the cut off for mildly depressed mood. The patients with FM were administered the ANT,<sup>5</sup> a neuro-psychological test that evaluates aptitude in attention and information processing; we have used the ANT in a previous study.<sup>23</sup>

Patients with FM were excluded from participation if they had taken a SNRI within 2 weeks of the study; had an active medical cause for their widespread pain; had a history of a psychotic disorder or a severe form of depression (eg, melancholic); or had a history of alcoholism, substance abuse, or an eating disorder within 5 years of intake. A positive urine toxicology or pregnancy test on the day of the neuroimaging scans was also exclusionary.

### Protocol for Ventricular Lactate Measurements by <sup>1</sup>H MRSI

All neuroimaging studies were conducted on a research-dedicated, multinuclear General Electric 3.0 T EXCITE MR system at the Citigroup Biomedical Imaging Center of Weill Cornell Medical College.

In vivo levels of ventricular lactate were obtained in all patients with a standard quadrature single-channel head coil using a multislice <sup>1</sup>H MRSI technique,<sup>4</sup> as fully described previously.<sup>15</sup> Briefly, multislice <sup>1</sup>H MRSI data were recorded from four 15-mm axial-oblique brain slices (Fig 2A) with the second most inferior slice traversing the lateral ventricles at the genu and splenium of the corpus

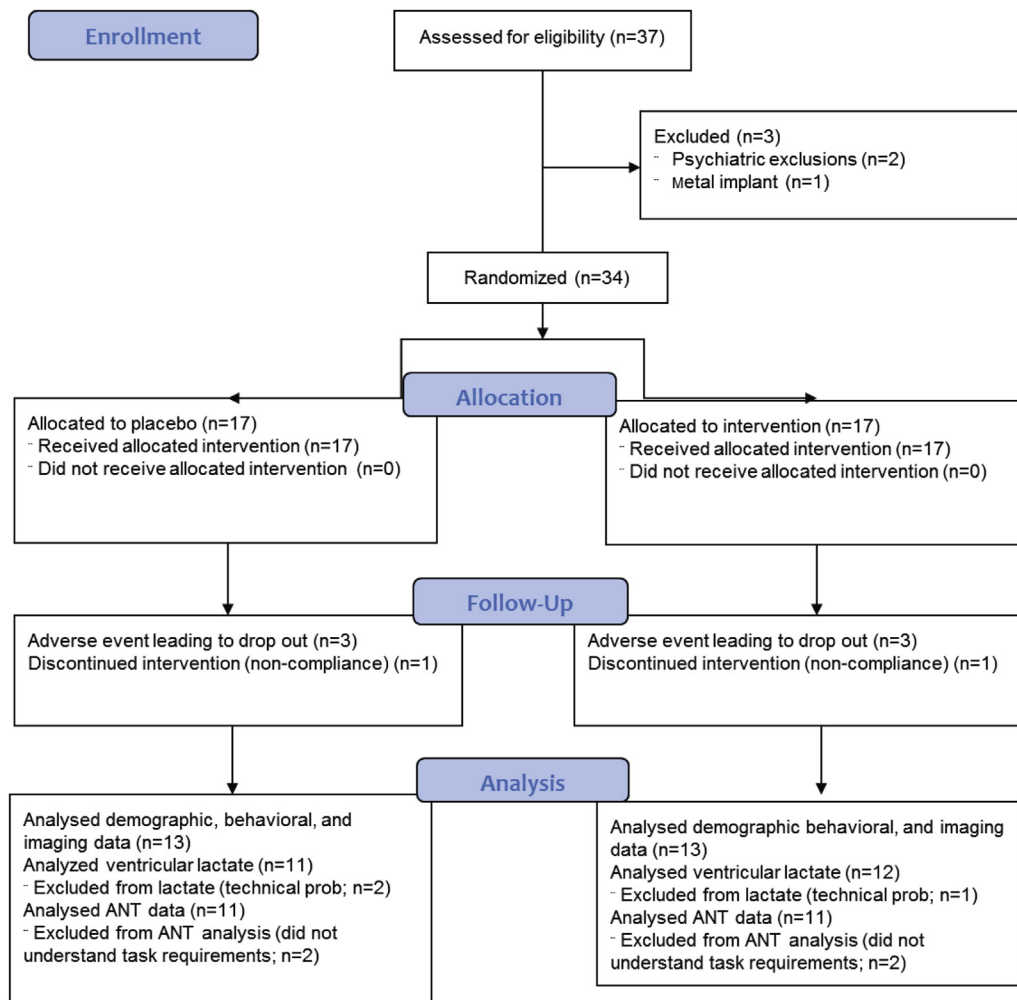


Figure 1. Consort statement.

callosum, using an echo time of 280 milliseconds, repetition time of 2300 milliseconds, a field of view of 240 mm,  $24 \times 24$  phase-encoding steps with circular k-space sampling, and 512 sample points; this yielded multiple voxels with a nominal size of  $1.0 \times 1.0 \times 1.5 \text{ cm}^3$ . The undesired pericranial lipid resonances were suppressed using octagonally tailored outer volume presaturation pulses.<sup>4</sup> Fig 2B shows representative spectra from a voxel in the lateral ventricle of a patient with no visible lactate peak (Fig 2B, trace a) and of a patient with FM with a clear lactate doublet peak visible at 1.33 ppm (Fig 2B, trace b). The lactate level data presented in this study are the mean values of the peak areas obtained for all voxels within the ventricular space.<sup>15,17,21</sup> For normalization of the levels across participants, the lactate peak areas were expressed in institutional units (i.u.) as ratios relative to the root mean square (rms) of the background noise in each spectrum – an approach that we have used previously in a number of studies.<sup>12,15,27</sup>

### Normative Ventricular Lactate <sup>1</sup>H MRSI Data

The normative ventricular lactate MRSI data for this study were derived by combining data previously

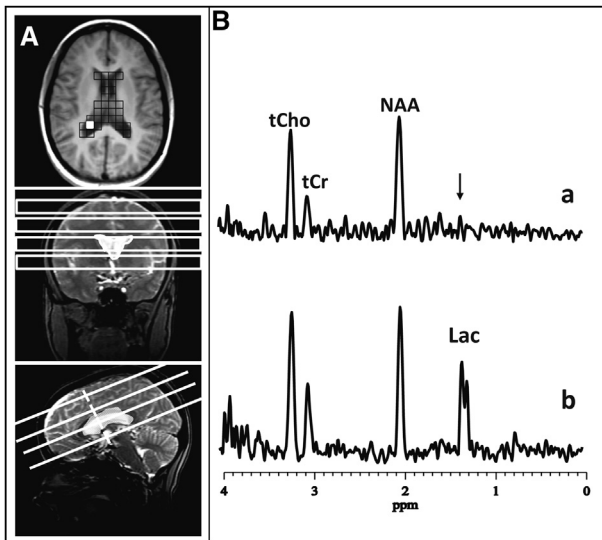
acquired and processed using methods identical to those described above from 11 healthy female individuals,<sup>17</sup> in addition to identically acquired and processed data from 6 healthy female individuals obtained as part of the present study, for a total sample of 17 female controls, after ensuring that the 2 datasets were statistically indistinguishable (Supplementary Fig 1 in the online supplement). Except for being physically and mentally healthy, these 17 normal female controls were group matched to the patients with FM on age and other demographic variables.

### Protocol for Cognitive Testing

The participants were given practice sessions to learn how to perform a simple motor reaction time task and then a cued flanker task, which allowed for manipulation of task difficulty.

Subsequently, data were collected during three 6-minute sessions each consisting of 96 randomly presented trials, as described previously.<sup>23</sup>

Information processing speed was computed for each participant by subtracting the median value of the simple reaction time (ie, reflecting motor response time) from the median reaction time for correct trials on the



**Figure 2.** (A)  $T_1$ -weighted human brain magnetic resonance (MR) images showing (top) a grid of lateral ventricular voxels of interest, and (middle and bottom) the location and angulation of the MRSI slices for optimal sampling of the lateral ventricular lactate (highlighted structure). The ventricular cerebrospinal fluid lactate data are the mean values obtained for all the voxels in the ventricular space represented by the grid on the top MR image. (B) Sample  $^1\text{H}$  MR spectra from a voxel in the right posterior horn of the lateral ventricle (filled box on top image in [A]) (a) in a patient without a visible lactate (Lac) peak and (b) in a patient with FM who showed a clear lactate doublet peak at 1.33 ppm. The other identified resonances are for *N*-acetylaspartate (NAA), total creatine (tCr), and total choline (tCho), which appear with greatly decreased intensity in ventricular spectra because they arise from partial volume averaging with surrounding brain tissue.

4 cue conditions of the ANT (no cue, center cue, double cue, and spatial cue). The executive control effect was calculated by subtracting the median reaction time of the congruent flanker conditions from the median reaction time of the incongruent flanker conditions.<sup>5</sup> Outcome variables chosen a priori based on our earlier work<sup>23</sup> were latencies in the no-cue condition and the computed executive control condition of the ANT.

### Treatment Protocol for Milnacipran or Placebo

After the baseline  $^1\text{H}$  MRSI scans at Weill Cornell Medical Center, participants were given either 2 bottles of milnacipran, the study medication, or 2 indistinguishable bottles of placebo. The first milnacipran bottle contained 12.5 mg tablets allowing for the recommended milnacipran dose ramp up protocol as follows: 1 pill at night on the first night, 1 pill twice a day on the second day, then 2 pills at night and 1 in the morning on the third and fourth days, then 2 pills twice a day on the fifth and sixth days. Then, on the seventh and eighth days, patients were instructed to take 2 pills in the morning and 4 pills at night, and finally 4 pills twice a day on the ninth day. Thereafter, they were instructed to move to the second bottle and to take 1 pill (ie, 50 mg) twice a day. Patients on placebo followed the same protocol.

After 8 weeks of taking either milnacipran or placebo, the patients returned to undergo the clinical and neuroimaging outcome assessments, which were identical to those conducted at baseline, except for the pain VAS for which the patients were queried about pain severity in the past week. In addition, participants were administered a “measure of certainty” questionnaire, which sought to determine their surety about whether they had been taking the real drug for which the responses were: 1, not at all sure; 2, somewhat unsure; 3, somewhat sure; 4, as sure as I can be. The “measure of certainty” test was administered a second time by telephone 2 weeks later.

### Statistical Data Analysis

#### Outcome Variables

The primary variables were baseline and post-treatment ventricular lactate levels, latencies in the no-cue condition, and the computed executive control condition of the ANT.

The secondary variables were change in pain and tenderness self-report and in the number of tender points, remaining signal conditions of the ANT, and changes in the questionnaires listed above.

Others measures included the measure of certainty, age, body mass index (BMI), and rate of psychiatric comorbidity.

#### Pain Measures

Because these measures were ordinal (VAS for pain and tenderness via a rating of pain with pressure on tender points), they were analyzed non-parametrically comparing the change in VAS and the change in tenderness (follow-up minus baseline) using Mann-Whitney U tests. Wilcoxon matched pairs tests were used to determine if pain for both measures decreased significantly for patients treated with milnacipran but not for those treated with placebo.

#### Ventricular Lactate

Baseline ventricular lactate values were used as the dependent variable in a general linear model (GLM) analysis comparing patients with FM with healthy controls. At the end of the study, ventricular lactate levels for patients treated with milnacipran were compared with those in healthy volunteers to test whether the treatment had been sufficient to normalize these levels.

Differences in age and BMI between healthy controls and patients with FM and between patients under the 2 treatment conditions were evaluated by independent samples *t*-tests. In the case of significant group differences or correlations between either of these variables and ventricular lactate within any group, these differences were used as covariates in the subsequent GLM analyses.

Other potential covariates that were examined for effects on baseline ventricular lactate for the patients with FM included a) illness diagnosis (FM only or FM with CFS), b) mode of onset (gradual vs sudden), c) presence or

absence of irritable bowel syndrome, d) current or lifetime psychiatric diagnosis, and e) use of medications other than milnacipran.

GLM analysis was used to assess the primary effect of treatment condition where baseline lactate served as a predictor variable, treatment condition served as the categorical variable, and follow-up lactate served as the dependent variable. Post hoc paired t-tests were performed to determine whether significant decreases at follow-up from baseline occurred.

### Relation Between Change in Lactate and Change in Pain

Spearman correlations were performed to examine the relationship between the change in lactate (follow-up minus baseline) and changes in the 2 pain measures (change from baseline for the total tenderness score and for the VAS of pain). Correlations were conducted with the 2 treatment conditions combined, and then for the placebo and drug conditions alone. A Fisher exact test was used to determine if the number of patients treated with the drug had more decreases in both lactate and pain at the end of the trial than those treated with placebo.

### ANT Statistical Analysis

GLM analysis was performed where a 2 (baseline/follow-up)  $\times$  4 (no cue, center cue, double cue, spatial cue) repeated measure design was used, with treatment as the categorical variable and past psychiatric history as a covariate because the latter had been found to affect the ANT results.<sup>23</sup> Overall effects were first evaluated, and univariate analyses were then applied for each ANT test. Each of the 4 cue conditions using baseline measures and past psychiatric history as covariates was analyzed using treatment condition as the categorical variable. The no-cue condition and executive motor function had been identified as variables of interest.

### Questionnaire and Self-Report Data

Because self-report questionnaire data were ordinal, nonparametric Mann-Whitney U tests were conducted on changes in values (follow-up minus baseline) for group comparisons for a) mood as assessed by the CES-D, b) perceived cognitive function as assessed by the MASQ, and c) general fatigue as assessed by the MFI. Spearman's correlations were used to test whether change in lactate predicted any of the above variables.

All tests were considered statistically significant at  $P \leq .05$ , 2-tailed.

## Results

### FM Sample Demographics and Characteristics

A total of 37 patients with FM signed written informed consent to participate in this study. Initial telephone psychiatric diagnostic evaluation with SCID identified 2 patients with melancholic depression, who were excluded. A third patient was excluded because of a

metallic implant incompatible with magnetic resonance imaging. Of the remaining 34 patients (33 women), 17 were randomized to the treatment arm and 17 to the placebo arm of the study (Fig 1). One person in each arm dropped out of the study for personal reasons, and 6 people dropped out due to side effects (3 in the placebo group and 3 in the drug-treated group). Therefore, a final sample of 26 participants (13 in each arm of the trial, all women) completed the study.

All 26 participants included in this report fulfilled the 1990 case definition for FM.<sup>29</sup> In addition, 11 of the 13 participants in the placebo group, and 7 of the 13 patients in the milnacipran group also fulfilled the 1994 case definition<sup>7</sup> for CFS. Six participants in the placebo group had a current Axis I psychiatric diagnosis (ie, within the past 6 months) compared with 2 in the milnacipran group; 7 participants in the placebo group were positive for a lifetime Axis I diagnosis compared with 10 in the milnacipran group. Seven participants in the placebo group and 8 patients in the drug group were off medications at the time of the study; the rest were taking medications for sleep, pain, and/or mood disturbance. None of these aforementioned variables differed between treatment groups.

At the end of the study, 5 participants on placebo gave certainty scores of 1 or 2, indicating their belief that they were receiving placebo. The remaining 8 gave scores of 3 or 4, indicating their belief that they were receiving the active drug. Two weeks after the end of the study, the numbers changed to 4 with scores of 1 or 2 and 9 with scores of 3 or 4. Thus, at the end of the study, 6 patients receiving the active drug indicated their belief that they were receiving placebo. The remaining 7 patients thought they were receiving the active drug. These numbers did not change in the data collected 2 weeks after the end of the study. Therefore, there was no difference in these measure of certainty data for patients taking placebo or active drug, indicating successful blinding, because the subjects were unable to determine whether being on active treatment was better than being on placebo.

Six participants on placebo and 4 patients on active drug had baseline CES-D scores of 16 or higher (indicating mild depression). Neither follow-up CES-D scores nor changes in these scores differed significantly between the 2 treatment groups. There was no effect of treatment on MASQ or MFI.

### Pain Analyses

Pain measures were evaluated on the full dataset (13 in the placebo-treated group and 13 in the milnacipran-treated group). The Wilcoxon matched pairs test revealed a significant difference in change in VAS pain for the milnacipran group versus the placebo group (mean [standard deviation] milnacipran =  $-1.24$  [1.57],  $n = 13$ , versus mean [SD] placebo =  $.66$  [1.75],  $Z = 2.43$ ,  $P = .014$ ,  $n = 13$ ) as well as a significant reduction for the milnacipran group in change in VAS pain from baseline (mean [SD] =  $6.43$  [1.54]) to follow-up (mean

**Table 1. Age and BMI Data for Controls and Patients Before Randomization and for Patients After Assignment to Milnacipran or Placebo**

PARAMETER	CONTROLS	PATIENTS	MILNACIPRAN	PLACEBO
Age, y $\pm$ SD	43.6 $\pm$ 7.0*	46.8 $\pm$ 11.6*	48 $\pm$ 11.6†	45.6 $\pm$ 11.1†
BMI, kg/m <sup>2</sup> $\pm$ SD	25.5 $\pm$ 4.3‡	27.4 $\pm$ 5.4‡	28.8 $\pm$ 6.0§	25.8 $\pm$ 4.4§

\* $t = -1.00$ ;  $P = .31$ .† $t = .50$ ;  $P = .62$ .‡ $t = 1.20$ ;  $P = .23$ .§ $t = 1.38$ ;  $P = .18$ .

[SD] = 5.18 [1.86],  $Z = 2.16$ ,  $P = .03$ ,  $n = 13$ ). The results were similar for the change in tenderness scores.

The tender point count was not affected by treatment (median = 18 before and after treatment for both conditions).

### Ventricular Lactate Levels

Normal control ventricular lactate levels were assessed in 6 healthy age-matched female participants (range = 6.4–7.8 i.u., median = 6.8 i.u.) and then combined with those previously acquired from 11 healthy age-matched female participants (range = 6.4–7.5 i.u., median = 6.8 i.u.), in an operation that was valid because the 2 dataset were found to be statistically identical (partial  $\eta^2 = .03$ ; see [Supplementary Fig 1](#)).

The <sup>1</sup>H MRSI data for 2 patients with FM on placebo and 1 patient in the milnacipran group were rejected due to excessive head motion during the scans, leaving 11 individuals in the placebo group and 12 in the treated group with analyzable ventricular lactate data. Inspection of the lactate values revealed 1 patient treated with placebo whose follow-up lactate value (18.13) was 4.5 standard deviations above the mean of the follow-up lactate values when treatment conditions were combined (8.76 [2.07],  $n = 22$ ). To demonstrate that the primary finding of the study was independent of this outlier, the treatment analysis was conducted both with and without this data point.

There was no significant difference in either age or BMI between the healthy controls and the patients with FM ([Table 1](#)).

Ventricular lactate was significantly higher in patients with FM ( $n = 23$ , mean [standard error] = 9.0 [.28] i.u.) than in controls ( $n = 17$ , mean [SE] = 6.73 (.32) i.u.,  $F_{1,37} = 22.96$ ,  $P = .000025$ , partial  $\eta^2 = .38$ ). Because BMI and lactate level correlated significantly for all participants (Pearson's  $r = .51$ ,  $n = 40$ ,  $P = .001$ ), the analysis was repeated with BMI as a covariate without an effect on the statistical significance of the results ( $F_{1,37} = 22.11$ ,  $P = .00004$ , partial  $\eta^2 = .37$ ).

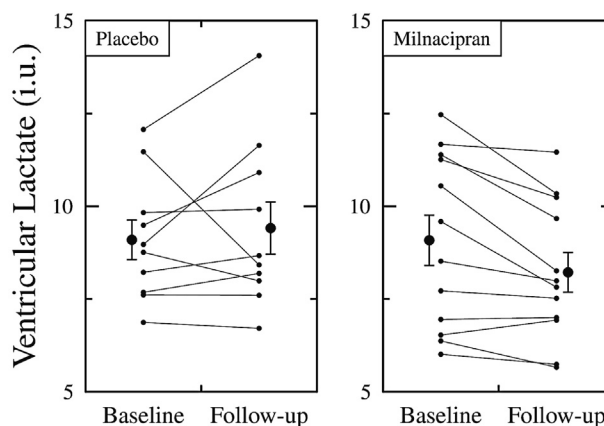
There was no significant difference in ventricular lactate levels between patients with FM + CFS compared with those with FM only ( $n = 17$ , 8.09  $\pm$  1.85 i.u. [SD] and  $n = 6$ , 9.44  $\pm$  1.9 i.u., respectively;  $F_{1,19} = 1.03$ ,  $P = .32$ ).

Neither age nor BMI differed significantly for the patients in the 2 treatment groups (see [Table 1](#)). The age of the participants, mode of illness onset, medication exposure at the start of the trial, and the presence or absence of comorbid diagnoses (irritable bowel syn-

drome, current or lifetime Axis I diagnosis) were not significant predictors of baseline ventricular levels.

Controlling for baseline lactate level and excluding the 1 outlier, follow-up lactate levels decreased in the milnacipran group compared with the placebo group ( $F_{1,19} = 5.19$ ,  $P = .034$ , partial  $\eta^2 = .21$ ). The association between BMI and baseline lactate level remained significant for the patient group ( $r = .75$ ,  $n = 22$ ,  $P < .0001$ ). After including BMI as a second covariate in the GLM analysis, the effect of treatment on ventricular lactate levels in milnacipran group versus the placebo group remained significant ( $F_{1,18} = 8.18$ ,  $P = .01$ , partial  $\eta^2 = .31$ ; [Fig 3](#)). Repeating the GLM analysis with the outlier included did not affect this result. Thus, the treatment effect was significant when covarying for BMI, with or without the outlier.

There was a significant decrease in ventricular lactate levels from baseline (mean [SD] = 9.08 [2.34] i.u.) to follow-up (mean [SD] = 8.21 [1.85] i.u.,  $t = 3.31$ ,  $df = 11$ ,  $P = .007$ ) for the milnacipran group. For the placebo group, there was no significant change in ventricular lactate levels from baseline (mean [SD] = 9.09 [1.67] i.u.) to follow-up (mean [SD] = 9.41 [2.28] i.u.,  $t = -.63$ ,  $df = 9$ ,  $P = .54$ ) with levels numerically higher on follow-up. Levels of ventricular lactate observed after



**Figure 3.** Ventricular lactate values for individual patients in institutional units (unadjusted means  $\pm$  standard error of the mean) before and after placebo or drug treatment; the outlier was not plotted. Using BMI and baseline lactate as covariates, the analysis revealed a significant effect of treatment group with the change in drug-treated ventricular lactate values decreased compared with the values for placebo and compared with levels found before active drug treatment.

milnacipran treatment remained higher than those in healthy controls ( $F_{1,26} = 6.00, P = .021$  corrected for BMI).

### Correlations Between Changes in Lactate Levels and Changes in Pain

There were significant associations for all patients with FM ( $n = 22, P < .05$ ) between change in ventricular lactate level and change in tenderness ( $\rho = .59$ ) and between change in ventricular lactate level and change in VAS pain ( $\rho = .54$ ). Examination of the scatterplot depicted in Fig 4 suggested the reason for the significant correlation. Discrete individual data points for the 2 groups show decreases in ventricular lactate level and pain for most patients treated with the drug (stippled area) at the end of the trial in contrast to most patients treated with placebo who show increases in ventricular lactate level or pain (outside the stippled area). Although the correlations between change in lactate level and pain at the end of the trial were not significant for either the placebo group or the drug-treated group, the pattern of response of individual patients within the 2 groups did differ significantly: 9 of 12 patients on milnacipran showed decreases in both lactate level and VAS pain compared with only 2 of 10 on placebo (see symbols in the stippled area in Fig 4; Fisher's exact test;  $P = .03$ ); the results were similar for the change in ventricular lactate level and the change in tenderness data (8 of 12 vs 2 of 10, respectively;  $P = .043$ ).

### Other Correlations

There were no significant correlations among any of the outcome variables or any of the questionnaire data.

### Cognitive Testing Results

There was no effect of age on baseline reaction time latencies. GLM analysis was not significant, so no further analyses of groups were done. However, effect size anal-

ysis did reveal a large partial  $\eta^2$  of .15<sup>2</sup>, suggesting that significance would be found with a larger sample size.

## Discussion

### Baseline Ventricular Lactate in Patients and Controls

This study has revealed that baseline ventricular lactate levels are increased in patients with FM relative to healthy controls, with a very large effect size.<sup>2</sup> Not only is this finding of increased ventricular lactate levels in FM consistent with the first hypothesis of this study, it is also analogous to a similar finding we previously reported in patients with CFS in 3 independent studies.<sup>15,17,21</sup> Ventricular lactate levels in patients with FM with or without comorbid CFS did not differ significantly from each other. That ventricular lactate levels have now been found to be increased in patients with both FM and CFS suggests that this variable may not have the specificity to serve as a biomarker for differentiating these 2 patient groups.

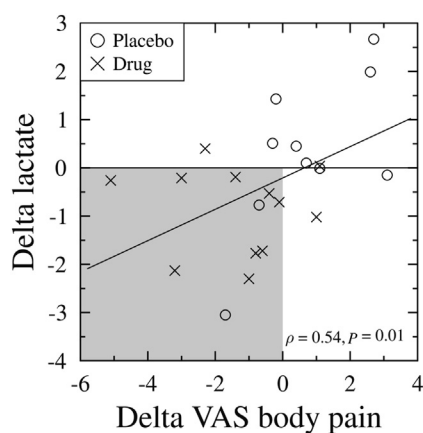
### Effects of Milnacipran and Placebo on Ventricular Lactate Levels

The second hypothesis of this study was that treatment with milnacipran, in comparison with placebo, would lower ventricular lactate levels. Patients with FM treated with milnacipran showed a significant decrease in ventricular lactate level on follow-up compared with the baseline level, with a large effect size, whereas the levels in the placebo group did not differ between the 2 time points (Fig 3). These findings persisted even after controlling for BMI (a potent predictor of baseline lactate level) and for the presence of a potential outlier. Ventricular lactate levels after treatment with milnacipran approached but remained statistically higher than those in healthy controls, indicating that drug treatment achieved only partial normalization. That ventricular lactate levels did not normalize is consistent with the presence of residual widespread pain after treatment.

Although the change in ventricular lactate level did not correlate with the change in pain for the patients treated with milnacipran over the course of the study, most of these patients showed decreases in both lactate level and pain, in contrast to most of those on placebo who showed increases in 1 or both of these variables (Fig 4). The finding of decreases in both pain and ventricular lactate level in the patients treated with milnacipran but not in those treated with placebo suggests the potential of ventricular lactate levels as an objective biomarker of therapeutic response in clinical trials of promising medications for FM.

### Pathophysiological Considerations

One potential common denominator that could produce reductions in both lactate level and pain may relate to a drug effect on glial activation. There is an emerging literature on the involvement of glial activation in chronic pain.<sup>10,16</sup> Interactions between activated glia and



**Figure 4.** Change in ventricular lactate versus change in VAS pain from the start to the end of the study for patients in the milnacipran and placebo groups. The overall correlation was significant ( $\rho = .54; P < .05$ ), an effect that was due to a different pattern of response between the groups with more drug-treated patients showing decreases in both variables in contrast to placebo-treated patients (compare number of Xs to Os in the shaded area).

neurons are thought to be important in the development of central sensitization,<sup>16</sup> a condition known to exist in FM.<sup>13</sup> A recent study supporting the existence of glial activation in FM reported large increases in cerebrospinal fluid interleukin (IL)-8 levels in FM,<sup>11</sup> thought to be released by activated glia. Release of lactate is a potential consequence of this central inflammatory state<sup>8,26</sup>; recent work linking lactate with central inflammatory states in disease<sup>14,30</sup> suggests that central lactate might serve as a proxy for inflammation. Turning off this state of glial activation may stop or reverse this inflammatory process.

The putative presence of such an activated central inflammatory state provides a possible mechanism by which treatment with milnacipran, a SNRI, might be therapeutic in FM. In addition to their established antidepressant properties, SNRIs have attracted attention for their potential anti-inflammatory and immunoregulatory properties.<sup>24,25</sup> Thus, it can be postulated that treatment with milnacipran may lower ventricular lactate levels in FM by targeting the underlying processes that may lead to glial activation and inflammation. Future research using magnetic resonance spectroscopy to measure ventricular lactate levels in synchrony with an appropriate positron emission tomography radioligand to assess neuroinflammation<sup>18</sup> could robustly test the validity of this hypothesis.

The data did not support the secondary hypothesis of this study that milnacipran would improve cognitive function as reflected by faster latencies on several tests of the Attention Network System. However, post hoc analysis indicated that the sample size was inadequate to detect effects induced by milnacipran on ANT tests.

### Study Limitations

This study has 2 notable limitations. The first relates to the characteristics and potential heterogeneity of the patient cohort. Most of the patients in the present FM

cohort met the criteria for both FM and CFS, which is not consistent with epidemiological studies that have shown FM to be approximately 10 times more common<sup>28</sup> than CFS.<sup>9</sup> This raises the possibility that the patients with FM in the present study might have been at the severe end of the illness spectrum compared with those with FM alone, because patients with both CFS and FM are generally more impaired than those with only CFS.<sup>1</sup> Although we found no difference in ventricular lactate levels between patients with FM only and those with FM + CFS, the relatively large proportion of patients with FM + CFS in this study may limit the generalizability of our results to the much larger number of patients who have FM without fulfilling the criteria for CFS. The second limitation of this study is the relatively small sample size; a larger sample size might have provided sufficient statistical power to detect the effect of the drug on cognitive function as assessed by the ANT.

In summary, the results of the present study indicate that ventricular lactate levels are increased in patients with FM compared with healthy controls and that the effects of treatment with milnacipran are a lowering of both ventricular lactate level and pain in FM. The postulated mechanism by which milnacipran, a SNRI, lowers ventricular lactate level and pain may involve targeting of the substrates of neuroinflammation, which has been postulated to occur in FM. Future studies investigating simultaneously the response of ventricular lactate and markers of inflammation to milnacipran in FM might robustly test this hypothesis and shed new light on the mechanism of action of this SNRI in treating FM.

### Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpain.2015.08.004>.

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