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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 (SNRI), is FDA-approved 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, FM patients have elevated ventricular lactate at baseline; (b) 8 weeks of treatment with milnacipran will lower ventricular lactate levels compared to both baseline and to placebo; and (c) treatment with milnacipran will improve attention and executive function in the Attention Network Test compared to 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 (^{1}H MRSI) was found to be higher in FM than in healthy controls [$F_{(1,37)} = 22.11$; $p < 0.0001$, partial $\eta^2 = 0.37$]. Milnacipran reduced pain in FM relative to placebo but had no effect on cognitive processing. At study end, ventricular lactate in the milnacipran-treated group decreased significantly compared to baseline and to placebo [$F_{1,18} = 8.18$, $p = 0.01$, partial $\eta^2 = 0.31$]. A significantly larger proportion of milnacipran-treated patients showed decreases in both ventricular lactate and in pain than placebo [$p = 0.03$]. These results suggest that ^{1}H MRSI measurements of lactate may serve as a potential

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biomarker for therapeutic response in FM and that milnacipran may act, at least in part, by targeting the brain response to glial activation and neuroinflammation.

Keywords

widespread pain; SNRI; brain function; magnetic resonance spectroscopy

INTRODUCTION

Milnacipran, a serotonin-norepinephrine reuptake inhibitor (SNRI) and an antidepressant, is FDA-approved 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 milnacipran was conducted in the disorder with two major outcome variables.

The first targeted outcome variable was ventricular lactate, which we hypothesized would be elevated in FM because we previously reported this metabolite to be elevated in patients with chronic fatigue syndrome (CFS)[15, 17, 21], another medically unexplained illness that shares extensive symptom overlap and coexists with FM in at least 35% of cases[1]. To test the validity of this assumption, proton magnetic resonance spectroscopic imaging (^{1}H MRSI) was used to measure ventricular lactate in patients with FM to determine whether it was elevated at baseline compared to normal control subjects, 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 drug-treated FM patients compared both to placebo-treated FM patients and to normal control subjects.

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)[5], a neuropsychological test that evaluates the subject's aptitude in attention and information processing, which are adversely affected in patients with CFS and FM[23]. This outcome measure was used to test a secondary hypothesis, which was that milnacipran will improve cognitive performance in treated FM patients compared to placebo.

METHODS

Subjects

Thirty seven subjects 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 subjects reported them to be at least a 2

on a 0 to 10 pain intensity, visual analog scale[19]. The presence of both widespread pain and 11 or more tender points fulfilled criteria for the diagnosis of fibromyalgia[29].

The total tenderness score for all enrolled subjects was derived by summing the rating of each positive tender point. Each participant was also asked to mark a 10-cm visual analog scale [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[7] and/or irritable bowel syndrome (IBS)[3], and whether their illness began suddenly or gradually. Following verification of the diagnosis of FM, each subject 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, subjects were randomized to either the drug or placebo condition to allow equal numbers in each. 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 Figure 1 for Consort diagram.

FM subjects underwent a telephone interview for psychiatric symptoms using the Structured Clinical Interview of DSM-IV (SCID)[6]. They also completed the following self-report questionnaires: the multi-dimensional fatigue inventory (MFI), a 20-item questionnaire scale[22] that provides data about “general fatigue” on a 1 to 5 scale for each question, where 1 is “yes, that is true” ranging to 5 which is “no, that is not true”; the Multiple Ability Self-report Questionnaire (MASQ), a 38-item questionnaire, which assesses perceived function in five cognitive domains[20] on a 1 to 5 scale 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 0 to 3 scale, where 0 is “rarely” and 3 is “most of the time”, with a total score of 16 being the cut off for mildly depressed mood. Lastly, FM subjects were administered the Attention Network Test (ANT)[5], a neuro-psychological test that evaluates aptitude in attention and information processing; we have used the ANT in a previous study[23].

FM subjects 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 (e.g., melancholic); or had a history of alcoholism, substance abuse or 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 ^{1}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.

Invivo levels of ventricular lactate were obtained in all subjects with a standard quadrature single-channel head coil using a multislice ^{1}H MRSI technique[4], as fully described previously[15]. Briefly, multislice ^{1}H MRSI data were recorded from four 15-mm axial-oblique brain slices (see Fig. 2A) with the second most inferior slice traversing the lateral ventricles at the genu and splenium of the corpus callosum, using: TE/TR 280/2300 ms, a

field of view 240 mm, 24×24 phase-encoding steps with circular k-space sampling, and 512 sample points; this yielded multiple voxels with a nominal size of 1.0×1.0×1.5 cc. The undesired pericranial lipid resonances were suppressed using octagonally tailored outer volume presaturation pulses[4]. Figure 2B shows representative spectra from a voxel in the lateral ventricle of a subject with no visible lactate peak (Fig. 2B, trace [a]) and of a patient with FM that shows a clear lactate doublet peak can be seen 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[15, 17, 21]. For normalization of the levels across subjects, 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[12, 15, 27].

Normative Ventricular Lactate ^{1}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 subjects[17], with identically acquired and processed data from 6 healthy female subjects obtained as part of the present study, for a total sample of 17 female subjects, after ensuring that the two data sets were statistically indistinguishable (see Figure 1S in the online supplement). Except for being physically and mentally healthy, these 17 normal female control subjects were group-matched to the FM patients on age and other demographic variables.

Protocol for Cognitive Testing

Subjects 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-min sessions consisting each of 96 randomly presented trials, as previously described[23].

Information processing speed was computed for each participant by subtracting the median value of the simple reaction time (i.e., reflecting motor response time) from the median reaction time for correct trials on the 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[5]. Outcome variables chosen a priori based on our earlier work[23] were latencies in the no-cue condition and the computed executive control condition of the ANT.

Treatment Protocol for Milnacipran or Placebo

Following the baseline ^{1}H MRSI scans at Weill Cornell Medical Center, participants were given either two bottles of milnacipran, the study medication, or two indistinguishable bottles of placebo. The first milnacipran bottle contained 12.5 mg tablets allowing for the recommended milnacipran dose ramp up protocol as follows: one pill at night on the first night, one pill twice a day on the second day, then 2 pills at night and one 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 one pill (i.e., 50 mg) twice a day. Patients on placebo followed the same protocol.

Following 8 weeks of taking either milnacipran or placebo, patients returned to undergo the clinical and neuroimaging outcome assessments, which were identical to those conducted at baseline, except for the pain visual analog scale 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—Primary: baseline and post-treatment ventricular lactate; latencies in the no-cue condition and the computed executive control condition of the ANT.

Secondary: change in pain and tenderness self-report and in number of tender points; remaining signal conditions of the ANT; changes in questionnaires listed above.

Others: Measure of certainty; age, body mass index (BMI); rate of psychiatric comorbidity

Pain Measures—Since these measures were ordinal (VAS of pain and tenderness via rating of pain with pressure on tender points), they were analyzed non-parametrically comparing the Δ VAS and Δ 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 milnacipran-treated but not for placebo-treated patients.

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

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

Other potential covariates that were examined for effects on baseline ventricular lactate for the FM subjects included: (a) illness diagnosis (FM only or FM with CFS), (b) mode of onset (gradual vs sudden), (c) presence or absence of IBS, (d) current or lifetime psychiatric diagnosis, and (e) use of medications other than milnacipran.

To assess the primary effect of treatment condition, GLM analysis was used where baseline lactate served as a predictor variable, treatment condition as the categorical variable, and

follow-up lactate 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 Δ lactate (follow-up – baseline) and the two Δ pain measures (change from baseline in the total tenderness score and in the VAS of pain). Correlations were conducted with the two treatment conditions combined, and then for the placebo and drug conditions alone. A Fisher's exact test was used to determine if the number of drug-treated patients had more decreases in both lactate and pain at trial end than placebo-treated patients.

ANT Statistical Analysis—GLM analysis was performed where a 2 (baseline/follow-up) x 4 (no-cue, center-cue, double-cue, spatial-cue) repeated measure design was employed, with treatment as the categorical variable and past psychiatric history as a covariate since the latter had been found to affect ANT results[23]. Overall effects were first evaluated, and univariate analyses then applied for each ANT test. Each of the four cue conditions using baseline measures and past psychiatric history as covariates was analyzed using treatment condition as 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 computed on Δ 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 employed to test whether Δ lactate predicted any of the above variables.

All tests were considered statistically significant at $p \leq .05$, two-tailed.

RESULTS

FM Sample Demographics and Characteristics

In the aggregate, 37 patients with FM signed a written informed consent to participate in this study. Initial telephone psychiatric diagnostic evaluation with SCID identified two subjects with melancholic depression, who were excluded. A third subject was excluded because of a MRI-incompatible metallic implant. Of the remaining 34 subjects (33 women), 17 were randomized to the treatment arm and 17 to the placebo arm of the study (Figure 1). One subject in each arm dropped out of the study for personal reasons, while 6 subjects 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 subjects included in this report fulfilled the 1990 case definition for FM[29]. In addition, 11 of the 13 subjects in the placebo group, and 7 of the 13 milnacipran group also fulfilled the 1994 case definition[7] for CFS. Six subjects in the placebo group had a current Axis I psychiatric diagnosis (i.e., within the past 6 months) compared to 2 of the milnacipran group; seven in the placebo group were positive for a lifetime Axis I diagnosis compared to

10 in the milnacipran group. Seven subjects in the placebo group and 8 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, five subjects 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, six subjects receiving the active drug indicated their belief that they were receiving placebo. The remaining 7 thought they were receiving the active drug. These numbers did not change in the data collected two 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, since the subjects were unable to determine whether being on active treatment was better than being on placebo.

Six subjects on placebo and 4 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 two treatment groups. There was no effect of treatment on MASQ or MFI.

Pain Analyses

Pain measures were evaluated on the full data set (13 placebo-treated and 13 milnacipran-treated subjects). Wilcoxon Matched Pairs Test revealed a significant difference in Δ VAS pain for the milnacipran versus placebo group [mean (SD) milnacipran = −1.24 (1.57) N = 13 versus mean (SD) placebo = 0.66 (1.75) N = 13; Z = 2.43, p = 0.014] as well as a significant reduction for the milnacipran group in Δ VAS pain from baseline [mean (SD) = 6.43 (1.54)] to follow-up [mean (SD) = 5.18 (1.86); Z = 2.16; p = 0.03; N =13]. The results were similar with the change in tenderness scores.

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 collected in 6 healthy age-matched female subjects [range 6.4 to 7.8 iu; median = 6.8 iu] and then combined with those previously acquired from 11 healthy age-matched female subjects [range 6.4 to 7.5 iu; median = 6.8 iu], in an operation that was valid because the two data set were found to be statistically identical (partial $\eta^2 = 0.03$; see Figure 1S in the online supplement)

The MRS data for two FM subjects on placebo and one subject in the milnacipran group were rejected due to excessive head motion during the scans, leaving 11 subjects in the placebo group and 12 in the treated group with analyzable ventricular lactate data. Inspection of the lactate values revealed one placebo-treated subject 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 control and FM subjects (see Table 1).

Ventricular lactate was significantly higher in patients with FM [N = 23; mean (SE) = 9.0 (0.28) i.u.] than in controls [N = 17; mean (SE) = 6.73 (0.32) i.u.; $F_{(1,37)} = 22.96$; p = 0.000025, partial $\eta^2 = 0.38$]. Because BMI and lactate correlated significantly for all subjects (Pearson's r = 0.51; N = 40; p = 0.001), the analysis was repeated with BMI as a covariate without an effect on the statistical significance of the result [$F_{(1,37)} = 22.11$; p = 0.00004, partial $\eta^2 = 0.37$].

There was no significant difference in ventricular lactate levels between patients with FM + CFS compared to those with FM only [N=17, 8.09 i.u. ± 1.85 (SD) and N=6, 9.44 i.u. ± 1.9, respectively; $F_{(1,19)} = 1.03$; p = 0.32].

Neither age nor BMI differed significantly for the patients in the two 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 (IBS, current or lifetime Axis I diagnosis) were not significant predictors of baseline ventricular levels.

Controlling for baseline lactate and excluding the one outlier, follow-up lactate decreased in the milnacipran compared to placebo treated group [$F_{(1,19)} = 5.19$; p = 0.034, partial $\eta^2 = 0.21$]. The association between BMI and baseline lactate remained significant for the patient group (r = 0.75, N = 22; p < 0.0001). After including BMI as a second covariate in the GLM analysis, the effect of treatment on ventricular lactate in milnacipran vs. placebo remained significant [$F_{1,18} = 8.18$, p = 0.01; partial $\eta^2 = 0.31$; see Figure 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 decline in ventricular lactate from baseline [mean (SD) = 9.08 i.u. (2.34)] to follow-up [mean (SD) = 8.21 i.u. (1.85); t = 3.31; df = 11; p =0.007] for the milnacipran group. For the placebo group, there was no significant change in ventricular lactate from baseline [mean (SD) =9.09 i.u. (1.67)] to follow-up [mean (SD) =9.41 (2.28); t = −0.63; df = 9, p = 0.54] with levels numerically higher on follow-up. Levels of ventricular lactate observed after milnacipran treatment remained higher than those in healthy controls [$F_{(1,26)} = 6.00$; p = 0.021 corrected for BMI].

Correlations between Δ Lactate and Δ pain

There were significant associations for all FM subjects [N = 22; p < 0.05] between Δ ventricular lactate and Δ tenderness [$\rho = 0.59$] and between Δ ventricular lactate and Δ VAS pain [$\rho = 0.54$]. Examination of the scatterplot depicted in Figure 4 suggested the reason for the significant correlation. Discrete individual data points for the two groups show decreases in ventricular lactate and pain for most drug-treated patients [stippled area] at the end of the trial in contrast to most placebo-treated patients who show increases in ventricular lactate

and/or pain [outside of the stippled area]. While the correlations between change in lactate and pain at the end of the trial were not significant for either placebo or drug treated groups, the pattern of response of individual patients within the two groups did differ significantly: Nine of 12 subjects on milnacipran showed decreases in both lactate and in VAS pain compared to only two of 10 on placebo (see symbols in stippled area in Figure 4; Fisher's exact test; $p = 0.03$); the results were similar for the Δ ventricular lactate and Δ tenderness data (8 of 12 vs 2 of 10, respectively; $p = 0.043$).

Other Correlations

There were no significant correlations among any of the outcome variables and 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 analysis did reveal a large partial η^2 of $.15^2$, 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 is elevated in FM relative to healthy control subjects, with a very large effect size[2]. Not only is this finding of elevated ventricular lactate in FM consistent with the first hypothesis of this study, it is also analogous to a similar finding we previously reported in CFS in three independent studies[15, 17, 21]. Ventricular lactate levels in FM patients with or without CFS comorbidity did not differ significantly from each other. That ventricular lactate has now been found to be elevated in both FM and CFS suggests that this variable may not have the specificity to serve as a biomarker for differentiating these two patient groups.

Effects of Milnacipran and Placebo on Ventricular Lactate Levels

The second hypothesis of this study was that treatment with milnacipran, in comparison to placebo, would lower ventricular lactate. Patients with FM treated with milnacipran showed a significant decrease in ventricular lactate on follow-up compared to baseline, with a large effect size, while the levels in the placebo group did not differ between the two time points (Figure 3). These findings persisted even after controlling for body mass index – a potent predictor of baseline lactate – 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 did not normalize is consistent with the presence of residual widespread pain after treatment.

While the change in ventricular lactate did not correlate with the change in pain for the drug-treated patients over the course of the study, most of these patients showed decreases in both lactate and pain, in contrast to most of those on placebo who showed increases in one or

both of these variables (Figure 4). The finding of decreases in both pain and ventricular lactate in the drug-treated but not in the placebo-treated patients 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 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[10, 16]. Interactions between activated glia and neurons are thought to be important in the development of central sensitization[16] – a condition known to exist in FM[13]. Supporting the existence of glial activation in FM is a recent study that reported large increases of cerebrospinal fluid interleukin (IL)-8 in FM[11] – thought to be released by activated glia. A potential consequence of this central inflammatory state is release of lactate[8, 26]; recent work, linking lactate with central inflammatory states in disease[14, 30], 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, an 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[24, 25]. It can thus be postulated that treatment with milnacipran may lower ventricular lactate in FM by targeting the underlying processes that may lead to glial activation and inflammation. Future research using MRS to measure ventricular lactate in synchrony with an appropriate positron emission tomography (PET) radioligand to assess neuroinflammation[18] 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 to detect milnacipran-induced effects on ANT tests.

Study Limitations

This study has two notable limitations. The first relates to the characteristics and potential heterogeneity of the patient cohort. The majority of subjects 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[28] than CFS[9]. This raises the possibility that the FM patients in the present study might have been at the severe end of the illness spectrum compared to those with FM alone, since subjects with both CFS and FM are generally more impaired than those with only CFS[1]. Although we found no difference in ventricular lactate between patients with FM only and those with FM + CFS, the relatively large proportion of the latter patients in this study may limit the generalizability of our results to the much larger number of patients who have FM without fulfilling criteria for CFS. The second limitation of this study is the relatively small sample size, which, if larger,

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 is elevated in patients with FM compared to healthy control subjects and that the effects of treatment with milnacipran are a lowering of both ventricular lactate and pain in FM. The postulated mechanism by which milnacipran, an SNRI, lowers ventricular lactate 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 Material

Refer to Web version on PubMed Central for supplementary material.

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Perspective

Patients treated with milnacipran showed decreases in both pain and ventricular lactate compared to 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.

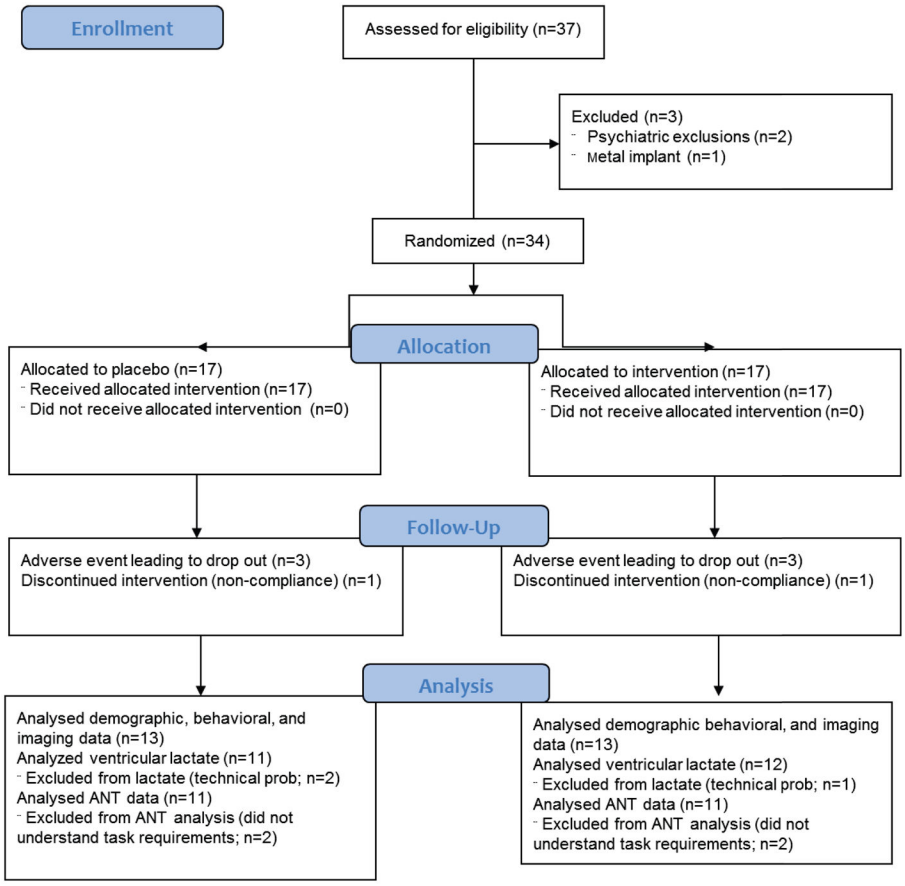

Figure 1.
Consort Statement.

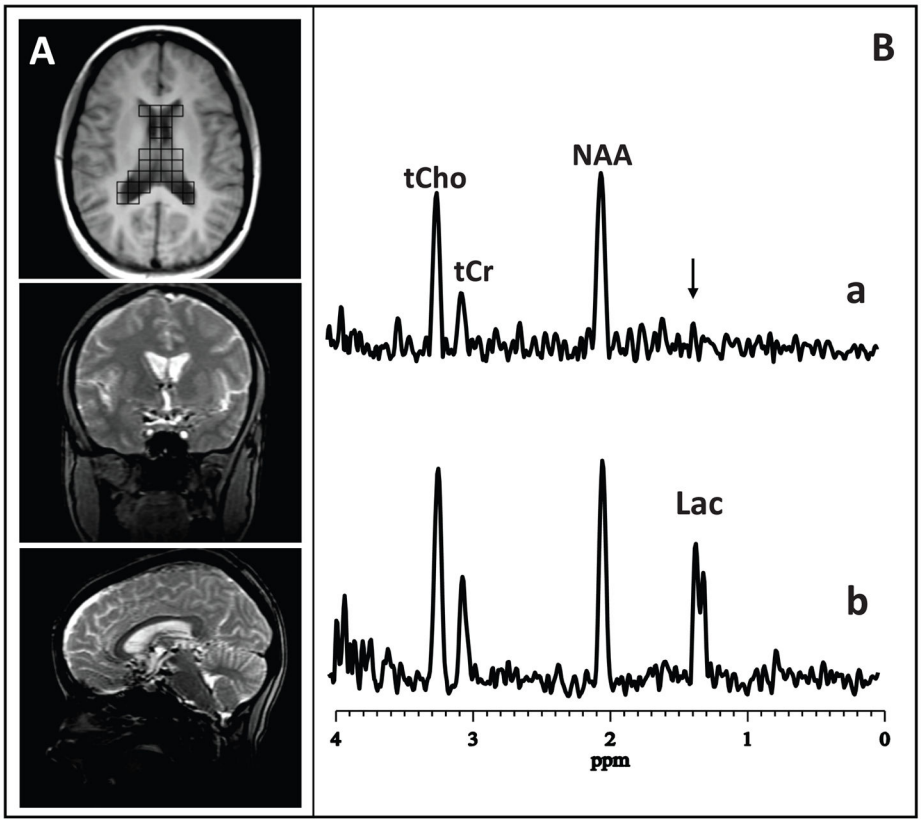

Figure 2.

[A] T_1-weighted human brain 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 presented ventricular cerebrospinal fluid lactate data are the mean value obtained for all the voxels in ventricular space represented by the grid on the top MR image. [B] Sample ^{1}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 subject 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.

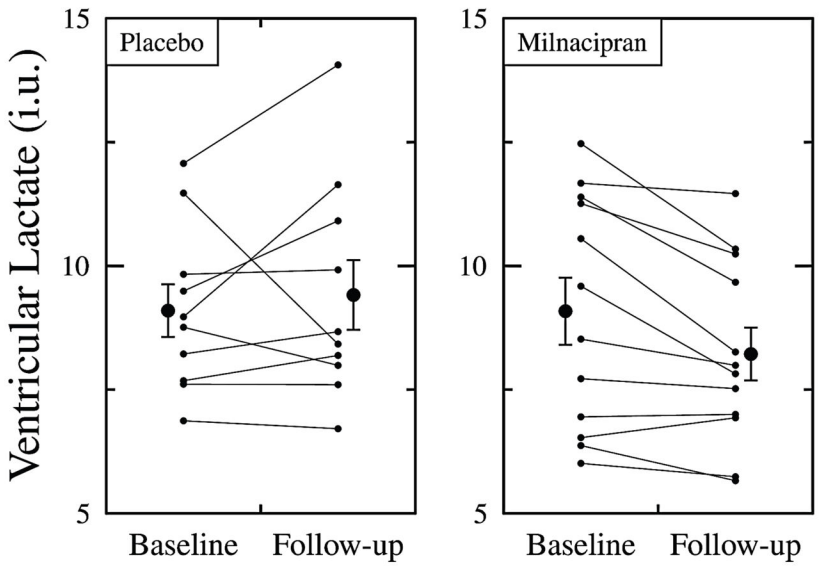

Figure 3.

Individual subject's ventricular lactate values in institutional units (unadjusted means ± SEM) before and after placebo or drug treatment; the outlier was not plotted. Using BMI and baseline lactate as covariates, analysis revealed a significant effect of treatment group with the change in drug-treated ventricular lactate values decreased compared to those of placebo as well as compared to levels found prior to active drug treatment.

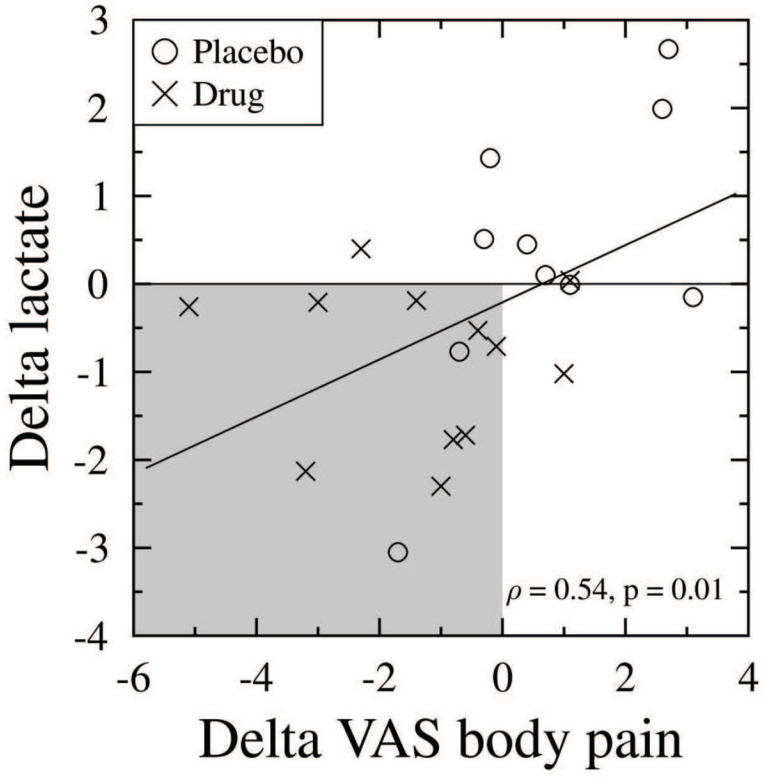

Figure 4.

Change in ventricular lactate versus change in VAS Pain from the start to end of the study for patients in milnacipran and placebo groups. The overall correlation was significant (ρ = 0.54; $p < 0.05$) – an effect which 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 stippled area).

Table 1

Age and BMI data for controls and patients prior to randomization and for patients after assignment to milnacipran or placebo

	Controls ± SD	Patients ± SD	Milnacipran ± SD	Placebo ± SD
AGE in years	43.6 ± 7.0*	46.8 ± 11.6*	48 ± 11.6**	45.6 ± 11.1**
BMI (kg/m^2)	25.5 ± 4.3•	27.4 ± 5.4•	28.8 ± 6.0••	25.8 ± 4.4••

* t = −1.00; p = 0.31

** t = 0.50, p = 0.62

• t = 1.20; p = 0.23

•• t = 1.38, p = 0.18