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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, 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.*

***Key words:** Widespread pain, serotonin-norepinephrine reuptake inhibitor, brain function, magnetic resonance spectroscopy.*

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Milnacipran, 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),[15,17,21] another medically unexplained illness that shares extensive symptom overlap and coexists with FM in at least 35% of patients.[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 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),[5] a neuropsychological test that evaluates the person'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 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.[19] The presence of both widespread pain and 11 or more tender points fulfilled the criteria for the diagnosis of FM.[29]

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[7] or irritable bowel syndrome,[3] 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).[6] They also completed the following self-report questionnaires: the Multidimensional Fatigue Inventory (MFI), a 20-item questionnaire[22] 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[20] 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,[5] a neuro-psychological test that evaluates aptitude in attention and information processing; we have used the ANT in a previous study.[23]

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 ^{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.

In vivo levels of ventricular lactate were obtained in all patients 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 (Fig 2A) with the second most inferior slice traversing the lateral ventricles at the genu and splenium of the corpus