ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 529–538
DOI 10.1002/art.37734

Low-Dose Naltrexone for the Treatment of Fibromyalgia

Findings of a Small, Randomized, Double-Blind, Placebo-Controlled, Counterbalanced, Crossover Trial Assessing Daily Pain Levels

Jarred Younger, Noorulain Noor, Rebecca McCue, and Sean Mackey

Objective. **To determine whether low dosages (4.5 mg/day) of naltrexone reduce fibromyalgia severity as compared with the nonspecific effects of placebo. In this replication and extension study of a previous clinical trial, we tested the impact of low-dose naltrexone on daily self-reported pain. Secondary outcomes included general satisfaction with life, positive mood, sleep quality, and fatigue.**

Methods. **Thirty-one women with fibromyalgia participated in the randomized, double-blind, placebo-controlled, counterbalanced, crossover study. During the active drug phase, participants received 4.5 mg of oral naltrexone daily. An intensive longitudinal design was used to measure daily levels of pain.**

Results. **When contrasting the condition end points, we observed a significantly greater reduction of baseline pain in those taking low-dose naltrexone than in those taking placebo (28.8% reduction versus 18.0% reduction; $P = 0.016$). Low-dose naltrexone was also associated with improved general satisfaction with life ($P = 0.045$) and with improved mood ($P = 0.039$), but not improved fatigue or sleep. Thirty-two percent of participants met the criteria for response (defined as a significant reduction in pain plus a significant reduction in either fatigue or sleep problems) during low-dose naltrexone therapy, as contrasted with an 11% response rate during placebo therapy ($P = 0.05$). Low-dose naltrexone was rated equally tolerable as placebo, and no serious side effects were reported.**

Conclusion. **The preliminary evidence continues to show that low-dose naltrexone has a specific and clinically beneficial impact on fibromyalgia pain. The medication is widely available, inexpensive, safe, and well-tolerated. Parallel-group randomized controlled trials are needed to fully determine the efficacy of the medication.**

Naltrexone, given at low dosages (in the range of 3–5 mg), has been demonstrated to reduce symptom severity in a small number of chronic conditions, including fibromyalgia (1), Crohn's disease (2,3), multiple sclerosis (4,5), and pruritus associated with systemic sclerosis (6). The use of naltrexone at this dosage range is typically referred to as low-dose naltrexone (7). As an orally available compound that is structurally similar to naloxone, naltrexone may work to reduce disease severity by attenuating inflammatory processes (8). This antiinflammatory effect is distinct from the better-known effect of naltrexone in the blockade of neuronal opioid receptors and may instead involve the antagonism of immune cell receptors, including microglia in the central nervous system (9,10).

Microglia are the resident macrophages of the central nervous system, and the primary form of immune defense in the brain and spinal cord. The cells normally exist in a resting (ramified) state but are activated by a range of triggers, including cell death, peripheral inflammation, and infection (11). Once activated, microglia undergo drastic morphologic changes and produce proinflammatory factors, such as cytokines, excitatory amino acids, and nitric oxide (12). These inflammatory factors can interact with neurons via multiple channels

ClinicalTrials.gov identifier: NCT00568555.

Supported by a grant from the American Fibromyalgia Syndrome Association, with additional support from Jim and Connie Binns, the Oxnard Foundation, the Chris Redlich Pain Research Endowment Fund, and the Rosekrans Pain Research Endowment Fund.

Jarred Younger, PhD, Noorulain Noor, BS, Rebecca McCue, BA, Sean Mackey, MD, PhD: Stanford University School of Medicine, Palo Alto, California.

Address correspondence to Jarred Younger, PhD, Department of Anesthesia, Stanford University School of Medicine, 780 Welch Road, Suite 207F, Palo Alto, CA 94304-1573. E-mail: jarred.younger@stanford.edu.

Submitted for publication January 2, 2012; accepted in revised form September 27, 2012.

(13) to cause hyperalgesia, fatigue, and other symptoms (14). The behavioral symptoms of activated microglia (classically called sickness behaviors) are very similar to the primary complaints of fibromyalgia, suggesting that activated microglia may underlie the condition. Fibromyalgia may therefore represent a state of hypersensitive microglial activity and heightened inflammation in the central nervous system. Compounds such as naltrexone, which are known to suppress microglial activity, may therefore be helpful in treating fibromyalgia. By antagonizing microglial activity (likely via action on Toll-like receptor 4), naltrexone may suppress the release of proinflammatory factors and thereby reduce pain and other symptoms of fibromyalgia.

In our previous small pilot trial, we found that 4.5 mg of naltrexone reduced self-reported symptoms of fibromyalgia (primarily daily pain and fatigue) (1). Fibromyalgia is a chronic pain condition that affects ~1–2% of the general population, with the large majority of diagnosed individuals being women (15). The disease is characterized by widespread musculoskeletal pain and sensitivity to mechanical pressure at defined tender points (16). Affected individuals also frequently experience symptoms such as profound fatigue, sleep difficulty, and problems with thinking, concentration, and memory (17). The cause of fibromyalgia is unclear and may encompass a number of distinct pathophysiologic profiles. Central sensitization and augmentation of pain are likely critical aspects of the pathophysiology of fibromyalgia (18,19).

Although demonstrating promising results, our early pilot study of low-dose naltrexone had 4 major limitations. The study was single-blind, was not counterbalanced, was of short duration, and was conducted in a small sample of 10 subjects. To verify our previous findings and to determine the suitability of low-dose naltrexone for larger randomized controlled trials, we conducted the present study. Our major goal for this project was to determine whether low-dose naltrexone had an impact on fibromyalgia pain that could not be attributed to placebo. To assess treatment-specific effects, we used an intensive longitudinal, crossover, no-washout design. Symptom severity reports were collected daily on handheld computers. By keeping participants and experimenters blinded to when the switch from placebo to low-dose naltrexone (or vice versa) occurred, we removed any external cues that could cause participants to shift their expectations.

We hypothesized that in contrast to placebo, low-dose naltrexone would be associated with significantly reduced severity of daily pain. We also hypothesized that low-dose naltrexone would beneficially affect the secondary outcomes of life satisfaction, mood, sleep quality, and fatigue.

PATIENTS AND METHODS

This study was registered with the ClinicalTrials.gov database (http://clinicaltrials.gov/) under identifier NCT00568555. Data were collected from April 21, 2008 to January 5, 2010.

Patient selection. Advertisements were made primarily via e-mails sent by the Fibromyalgia Network (http://www.fmnetnews.com) to registered individuals in Northern California. Interested individuals completed a web-based survey to determine initial eligibility. Participants passing the initial eligibility test were contacted via phone for additional screening and were invited to come to the laboratory for a more detailed screening. Women between the ages of 18 and 65 years who lived within a 2-hour drive of the laboratory were invited to participate in the study. All study participants met the American College of Rheumatology 1990 diagnostic criteria for fibromyalgia (16).

Tender point examinations were conducted by the lead investigator (JY) and supervised by the medical advisor (SM), using a JTech Commander digital algometer (JTech Medical). Individuals were excluded from the study if they demonstrated evidence of joint inflammation or reported any history of rheumatic or autoimmune disease. Participants also submitted a blood sample at the screening visit and were excluded from further participation if the following thresholds were met: rheumatoid factor (RF) >20 IU/ml, antinuclear antibody (ANA) titer >1:80, erythrocyte sedimentation rate (ESR) >60 mm/hour, or C-reactive protein (CRP) level >2 mg/dl. Individuals presenting with significant psychiatric distress or a score of >29 on the revised Beck Depression Inventory (BDI-II) were excluded from the study.

Participants taking opioid analgesic medications (including atypical opioids such as tramadol) were excluded from the study. Opioid medications were excluded because naltrexone is an opioid antagonist and could potentially cause opioid withdrawal. Study participants were allowed to continue all existing medications throughout the study protocol. Participants who had recently changed their medications were not allowed to begin the study protocol until their other treatments had been taken at steady dosages for at least 2 months. Participants were instructed to keep other medications at stable dosages throughout the trial and to report any actual or potential changes in their treatment regimen to the research personnel.

Baseline questionnaires. Fibromyalgia severity at baseline was gauged with the Fibromyalgia Impact Questionnaire (FIQ) (20). The FIQ yields a range of scores from 0 to 100. A score of 50 indicates average fibromyalgia severity, and a score of 70 and above demonstrates severe symptom severity.

Depressive symptoms at baseline were assessed with the BDI-II (21), a widely used measure of depression. Scores of 0–13 indicate no-to-minimal depression, 14–19 mild depression, 20–28 moderate depression, and 29–63 severe depression.

Study design. We used a randomized, double-blind, placebo-controlled, crossover design for this study (Figure 1). Procedures were approved by the Institutional Review Board

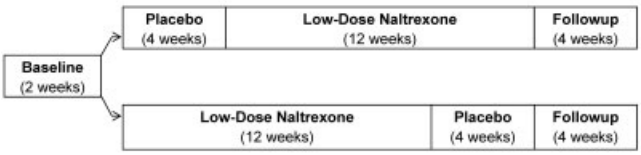


Figure 1. Outline of the study protocol.

at Stanford University School of Medicine, and all participants provided written informed consent.

Participants started the protocol with a 2-week baseline period, during which time no capsules were administered. Participants then randomly entered the placebo-first or low-dose naltrexone–first arms of the study. After completing the placebo or low-dose naltrexone condition, participants were immediately switched to the other condition. The protocol duration was 22 weeks per participant. To minimize attrition during the lengthy study, the placebo condition was designed to be shorter than the low-dose naltrexone condition (4 weeks versus 12 weeks). Also, no washout period was used between the low-dose naltrexone and placebo conditions. The exclusion of a washout period also allowed us to keep participants blinded with regard to the time at which crossover occurred. By removing any cues that one compound was being switched to the other, we could be more certain that any changes in pain that occurred after the switch were due to pharmacologic effects and not to changing expectations.

Following the completion of both the low-dose naltrexone and placebo stages, participants completed a 1-month followup period. Daily reports were maintained throughout the followup period, as our group of investigators and others have observed symptoms to remain suppressed after stopping low-dose naltrexone (1,2). Participants visited the laboratory every 2 weeks to retrieve additional capsules and to report side effects. During the laboratory visits, participants also guessed whether they had been receiving placebo or low-dose naltrexone over the previous 2 weeks. They also completed tests of mechanical pain sensitivity and heat pain sensitivity (data not shown). Participants were compensated $30 at each laboratory visit, for a total of $360.

Treatment and blinding. The drug capsules contained 4.5 mg of naltrexone hydrochloride mixed with a microcrystalline filler and noncaloric sweetener in a standard opaque gelatin capsule. The 4.5-mg dose was chosen because it is the dose typically used in other clinical trials (2,3). Placebo capsules contained only the filler and sweetener. All capsules were compounded by Preuss Pharmacy. Quality control testing was provided by Front Range Laboratories.

Study participants were randomly allocated to one of two medication lines by a random number generator software program. Subjects were then assigned to the medication line by 2 researchers who were not otherwise associated with the study. All study personnel were blinded with regard to the randomization assignment. Medication lines were contained in sequentially numbered containers to conceal the contents, and randomization information was kept in a sealed envelope until all participants completed the protocol. During the placebo and drug conditions, participants took 1 capsule daily, ~1 hour before bedtime. Study participants and study personnel working directly with them were kept blinded with regard to the crossover details of the study design (e.g., the different durations of the placebo and low-dose naltrexone conditions and the time points at which a crossover might occur).

Daily assessments. Throughout the entire protocol (baseline, placebo, low-dose naltrexone, and followup), participants completed daily symptom reports using a Palm Z22 handheld computer and the freely available Experiential Sampling Program (http://www.experience-sampling.org/). Symptom reports were completed before bedtime. The devices recorded the time and date of each survey completion, which was used to eliminate cases of retrospective reporting. The primary outcome of daily pain was assessed with the question, "Overall, how severe has your pain been today?" A 0–100 sliding-bar scale was used for recording responses, with 0 anchored as "no pain at all" and 100 as "worst pain imaginable." Questions assessing secondary outcomes used a similar 0–100 scale. Medication tolerability was measured via a 0–100 scale with 0 anchored as "cannot tolerate at all" and 100 as "tolerate perfectly well."

Baseline pain severity was calculated for each participant by averaging pain reports across all 14 days in the baseline condition. Raw pain scores were reported on a 0–100 scale. End points for the placebo and low-dose naltrexone conditions were calculated by averaging pain reports during the final 3 days of each condition. Those values were then converted to percentage of pain reduction from baseline, using the following formula: [(baseline pain − end point pain)/baseline pain] × 100.

Secondary outcomes were selected based on the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (22) and included life satisfaction, mood, sleep quality, and fatigue. These outcomes were measured on single-item visual analog scales, similar to the primary pain outcome.

Statistical analysis. All analyses were conducted using SPSS version 19 software. The primary clinical end point was self-reported daily pain. Because this study used an intensive longitudinal design, assumptions of independent and identically distributed residuals could not be made, and therefore, the proper modeling of data interdependency across time was an important concern. To test all models, the linear mixed model (LMM) approach was used. The LMM allows for correlated observations in the dependent variable. Denominator degrees of freedom were estimated via SPSS conventions when using LMMs with repeated-measures data.

To test the primary clinical outcome, the percentage of change in the level of pain from baseline was entered as the dependent variable, and the study day was entered as the repeated index. The optimal working correlation matrix for repeated measures was determined by contrasting the available options with the Bayesian information criterion, with autoregressive (AR1) as the default structure. Baseline pain was calculated by averaging pain across the entire 14-day baseline period. To contrast the placebo and low-dose naltrexone conditions, the percentage of pain reduction from baseline was assessed during the final 3 days of each treatment condition. Condition (placebo versus low-dose naltrexone) was entered as a fixed factor. Also, group designation (receiving placebo first or low-dose naltrexone first) was entered as a fixed factor, as was the condition × group (order effect) interaction. The subject ID number was entered as a random effect.

Two control variables were also tested in the model. First, baseline pain severity was entered. The baseline pain con-

trol variable was designed to determine if individuals with greater baseline severity were more likely to respond to placebo or low-dose naltrexone. Second, a linear time function was entered. The time variable was included to determine if change in pain could be attributed simply to natural improvement over time. The time variable was created by entering the observation day (days 1–140) for each outcome data point. The time variable was tested in a separate model in order to properly include the entire longitudinal data set, and to avoid artificial overlap with the condition × group interaction. The modeling approach was repeated for all secondary outcomes.

Response rate was calculated as a final secondary outcome. Response rate describes the percentage of participants that are likely to respond to the medication. To calculate the response rate, we used the conservative methods proposed by Arnold and colleagues (23). To be designated a responder, an individual had to demonstrate at least a 30% reduction in pain, as well as either a 30% reduction in fatigue or a 30% improvement in sleep. Differences in response rate between the placebo and low-dose naltrexone conditions were statistically assessed with a chi-square test.

RESULTS

Participants. A total of 325 women completed the web survey. The majority were excluded because of excessive distance from the study site (Figure 2). Thirty-one women were eligible for the study, signed consent forms to participate, and were randomized to the low-dose naltrexone–first or placebo-first conditions. Demographic information is provided in Table 1. Participants had moderate symptom severity, as measured by the FIQ, and minimal-to-moderate levels of depressive symptoms based on the BDI-II. Their mean ESR was within the normal range. All enrolled participants had negative or below-detectable levels of RF and ANA. Three participants had detectable, but minimal, levels of CRP (1.1, 1.6, and 1.6 mg/dl, respectively). The majority of participants were taking at least 1 other medication (Table 1).

Dropouts and missing data. One participant dropped out of the study during the first 3 days of taking capsules. This subject complained of dryness (eyes and mouth) and tinnitus. No usable data were obtained from this individual, and she was excluded from all analyses. She was taking low-dose naltrexone. One participant dropped out immediately after being switched from low-dose naltrexone to placebo because she perceived she had been switched to placebo and wanted to pursue taking low-dose naltrexone clinically. Because no placebo data had been collected, she was not included in the analyses.

Problems with the handheld computer caused a loss of baseline data for 1 participant. She was excluded from the analyses. Therefore, of the 31 women who consented for the study, 28 had sufficient data to be included in all analyses.

Assessment of blinding efficacy. At each laboratory visit, participants were asked to guess whether they had been taking placebo or low-dose naltrexone for the previous 2 weeks. Each participant was allowed 8 guesses (2 during the placebo condition and 6 during the low-dose naltrexone condition). During the placebo condition, 52% of the guesses were accurate (with 48% wrongly guessing low-dose naltrexone). During the drug condition, 44% of the guesses were accurate (with 56% wrongly guessing placebo). Guess accuracy did not diverge significantly from chance ($\chi^2 = 0.39$, $P = 0.532$).

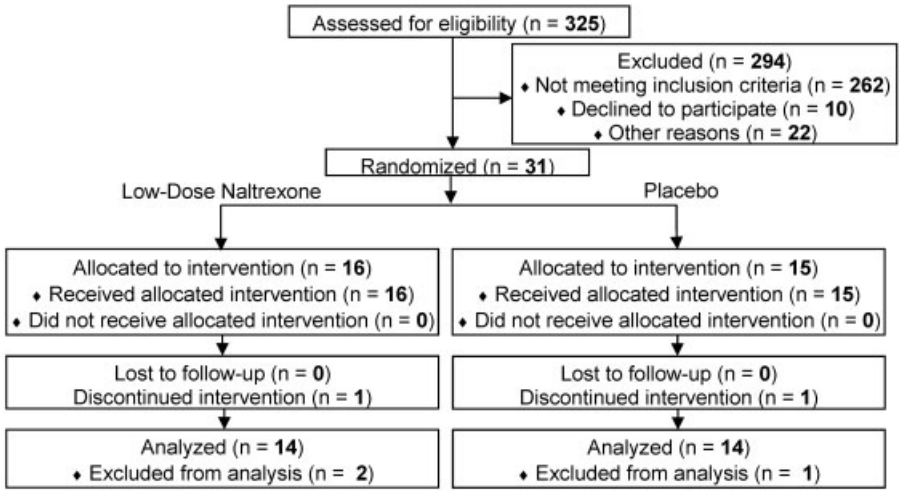


Figure 2. Flow diagram showing the distribution of the study subjects from initial assessment to analysis of study data. Details given according to the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting randomized controlled trials.

Table 1. Demographic and clinical features and concomitant medication use in the entire study sample as well as the two treatment groups*

	All patients (n = 28)	Placebo first (n = 14)	Low-dose naltrexone first (n = 14)
Demographic and clinical features, mean ± SD (range)			
Age, years	42.7 ± 12.9 (23–65)	42.3 ± 13.0	43.8 ± 13.4
Duration of illness, years	11.7 ± 10.1 (0.7–44)	13.6 ± 11.3	8.3 ± 8.0
Fibromyalgia severity, by FIQ	57.2 ± 11.8 (29–76)	55.6 ± 13.0	58.9 ± 10.6
Depression, by BDI-II	12.8 ± 7.4 (2–28)	9.7 ± 6.0	16.0 ± 7.5
Body mass index, kg/m^2	27.5 ± 5.6 (18–38)	26.4 ± 5.2	30.0 ± 5.7
ESR, mm/hour	11.8 ± 7.6 (0–36)	9.6 ± 5.5	15.21 ± 8.2
Concomitant medication use			
No. taking other drugs			
No other drugs	3	–	–
1 other drug	16	–	–
2 other drugs	6	–	–
3 other drugs	4	–	–
4 other drugs	1	–	–
5 other drugs	1	–	–
No. taking other classes of drugs			
Anticonvulsant	5	–	–
SSRI	5	–	–
SSNRI	4	–	–
Tricyclic antidepressant	4	–	–
Benzodiazepine	4	–	–
Estrogen derivative	3	–	–
Protein pump inhibitor	3	–	–
Nonbenzodiazepine hypnotic	3	–	–
Muscle relaxant	2	–	–
Thyroid supplement	2	–	–
Statin	1	–	–
Inhaled β_2-agonist	1	–	–
Angiotensin II blocker	1	–	–
Antiviral agent	1	–	–
Antimigraine	1	–	–
Histamine antagonist	1	–	–

* FIQ = Fibromyalgia Impact Questionnaire (≥70 represents severe symptoms); BDI-II = Beck Depression Inventory II; ESR = erythrocyte sedimentation rate; SSRI = selective serotonin reuptake inhibitor; SSNRI = selective serotonin and norepinephrine reuptake inhibitor.

Daily pain severity (primary outcome). The difference in pain reduction between the low-dose naltrexone and placebo conditions was tested by contrasting the final 3 days in each condition (Table 2). For the entire study group, pain at the end of the placebo condition was reduced by 18.0 ± 10.8% (mean ± 95% confidence interval). At the end of the low-dose naltrexone condition, pain was reduced by 28.8 ± 9.3%. The difference in pain reduction between placebo and low-dose naltrexone was significant ($F[1,30] = 6.4$, $P = 0.016$). There was no significant main effect for assignment in the placebo-first versus the low-dose naltrexone–first group ($F[1,26] = 0.1$, $P = 0.710$) and there was no condition × group interaction ($F[1,34] = 0.02$, $P = 0.899$).

Baseline pain severity interacted significantly with study condition ($F[1,29] = 4.3$, $P = 0.047$). Post hoc analyses (correlation coefficient) revealed that those with greater baseline pain were marginally more likely to experience a placebo-induced reduction of pain

Table 2. Change in daily pain scores (primary outcome variable), by treatment group*

Study group	Pain score at baseline	Change in pain score with treatment: Placebo	Change in pain score with treatment: Low-dose naltrexone
Placebo first	50.0	−10.7 (−19.4)	−16.6 (−31.5)
Low-dose naltrexone first	51.5	−11.7 (−16.5)	−14.3 (−26.0)
All subjects	50.8	−11.2 (−18.0)	−15.5 (−28.8)

* Pain severity was assessed in each patient during the final 3 days in each treatment condition, with the use of a 0–100 visual analog scale (where 100 is the most severe pain). Change scores are the number (%) difference from baseline; negative values indicate improvement.

($r = -0.36$, $P = 0.056$). Baseline pain severity, however, was not associated with pain change due to low-dose naltrexone ($r = 0.11$, $P = 0.57$). The linear time variable, which was tested separately, was not a significant predictor of change in pain compared with baseline ($F[1,148] = 0.04$, $P = 0.836$).

To check the stability of the findings given the high intrinsic variability of pain reports, the analyses were repeated using the last 7 days in each condition (instead of the last 3 days). The difference between placebo and low-dose naltrexone remained significant ($F[1,66] = 12.3$, $P = 0.001$).

Secondary outcomes (life satisfaction, mood, sleep quality, and fatigue). Separate models were also performed for the 4 secondary outcomes. All models included baseline scores, as well as linear effects of time, as control variables.

Patients' general satisfaction with life was significantly increased in the low-dose naltrexone condition as compared with placebo (11.1% versus 3.2%; $F[1,34] = 4.3$, $P = 0.045$). Mood was also significantly improved in the low-dose naltrexone condition compared with placebo (10.7% versus 2.1%; $F[1,37] = 4.6$, $P = 0.039$). No other predictors in the models predicted significant variance in pain outcome.

There was no significant difference in sleep quality between the low-dose naltrexone and placebo conditions (10.4% improvement versus 9.2%; $F[1,31] = 0.3$, $P = 0.575$). Also, there was no significant difference in fatigue in the two groups (12.6% reduction versus 7.8%; $F[1,59] = 0.55$, $P = 0.461$). Other predictors in the model also failed to predict significant variance in the secondary outcomes.

Side effects. Tolerability of low-dose naltrexone was rated 89.2 ± 15.1 (mean ± SD), and placebo tolerability was rated 89.4 ± 15.6. Fixed-effects analyses revealed no difference in tolerability between the active drug and placebo ($F[1,502] = 0.058$, $P = 0.809$). Table 3 displays the percentages of participants reporting each side effect, by drug condition. Pearson's chi-square tests (not corrected for multiple comparisons) were performed on all reported side effects to see if the frequency of complaints occurred more in the low-dose naltrexone condition than placebo. Only two side effects, vivid dreams ($\chi^2 = 4.4$, $P = 0.037$) and headache ($\chi^2 = 4.05$, $P = 0.044$), were more frequently reported in the low-dose naltrexone condition. Increased vividness of dreams was the most commonly reported side effect in both the placebo and low-dose naltrexone groups (13% and 37% reporting the effect, respectively). Rarely, participants described the vivid dreams as unpleasant.

Table 3. Reported side effects, by treatment group*

Side effect	Placebo	Low-dose naltrexone
Vivid dreams	13	37†
Headache	3	16‡
Nausea/upset stomach	7	16
Nightmares	3	13
Insomnia	10	16
Dry mouth or dry throat	3	10
Shortness of breath	0	3
Anxiety	0	3
Agitation	0	3
Increased hair growth	0	3
Increased sweating	0	3
Weight gain	3	0
Dizziness	3	3

* Values are the percentage of participants reporting each side effect.
† $\chi^2 = 4.36$, $P = 0.037$.
‡ $\chi^2 = 4.05$, $P = 0.044$.

All participants were told that they had the option to reduce their daily dosage to 3.0 mg if they experienced side effects. Four individuals requested the 3.0-mg dosage. Three of those individuals were taking low-dose naltrexone at the time of the request; 1 reported having headaches, 1 reported heartburn, and 1 reported irritability. Another individual who requested a dosage reduction due to headaches was taking placebo. In all cases, the severity of side effects was reduced by the change in dosage.

Response rate. In the low-dose naltrexone condition, 9 individuals (32%) met all criteria for a positive response. In the placebo condition, 3 individuals (11%) met all criteria. The difference in response rates was significant ($\chi^2 = 3.82$, $P = 0.05$).

DISCUSSION

In this study, we found evidence that daily treatment with naltrexone (3.0–4.5 mg) reduces pain associated with fibromyalgia syndrome. The results largely support our earlier preliminary work (1), further suggesting a potential role of low-dose naltrexone in the treatment of fibromyalgia. The average reduction in pain we observed after 12 weeks of low-dose naltrexone administration was 28.8%, which was slightly lower than the average 32.5% reduction observed in our first trial. The percentages of participants who exhibited at least a 30% reduction in pain levels was very similar between the two studies, with a 57% pain response rate in the current study and a 60% response rate in the previous study. Unlike the first study, however, we did not find an effect of low-dose naltrexone on fatigue. The collective results suggest that low-dose naltrexone likely reduces

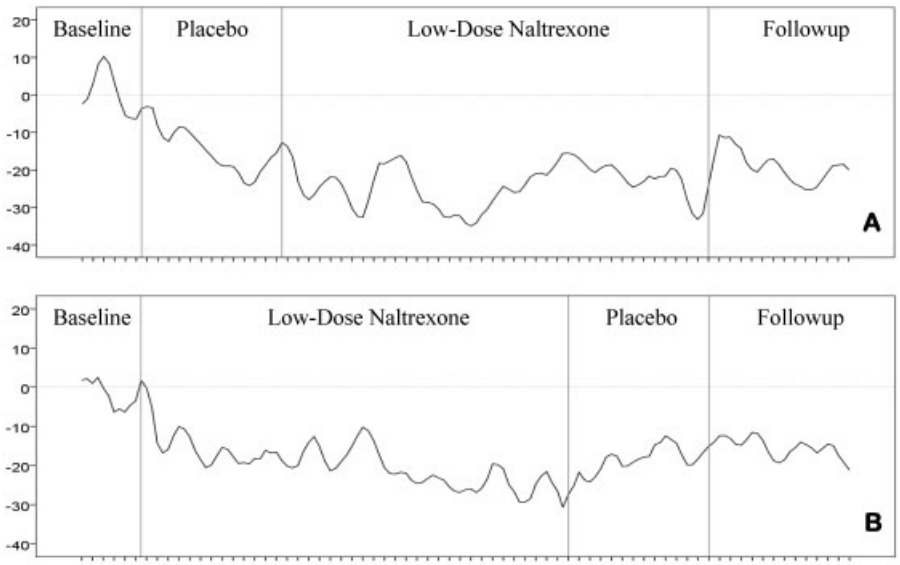


Figure 3. Average pain response of participants in **A,** the placebo-first group and **B,** the low-dose naltrexone–first group. Graphs show the average daily pain values across the entire study period, with a 3-day smoothing filter. The x-axis represents the day of the study; the y-axis represents the percentage of baseline pain. For the purposes of illustration in order to fit all participants' data on the same scale, extra data were truncated for participants who completed extra study days.

pain levels to a greater degree than placebo and may also improve mood and general satisfaction with life.

The study drug was well-tolerated by the majority of participants. Using daily ratings of tolerability (0–100 scale), there was no difference between the tolerability of low-dose naltrexone and placebo. Two side effects, vivid dreams and headache, were reported more often when the subjects were taking low-dose naltrexone than when they were taking placebo. Side effects were minimized by reducing the dosage to 3.0 mg/day.

Low-dose naltrexone is a compound that may reduce fibromyalgia disease severity via the novel action of microglia antagonism (8). We hypothesize that in conditions such as fibromyalgia, microglia (as well as other glial cells) may be abnormally sensitized (24). This microglia priming could be the result of normal aging (25), environmental insult (26), previous immune insult (27), or peripherally derived immune activators (28,29). In the primed state, microglia can be provoked to release proinflammatory factors in the brain and spinal cord (25). Upon release, these proinflammatory factors may then interact with neurons, leading to the central facilitation of pain processing (30–34). Unfortunately, microglia cells are not available for direct interrogation in living humans, making direct evidence for the microglia hypothesis difficult to collect. We note that there are alternative explanations for the mechanism of action of low-dose naltrexone, including the hypothesis that transient opioid blockade leads to a compensatory, long-lasting increase in endogenous opioid activity (35–37). Given that some research has identified endogenous opioid dysregulation in patients with fibromyalgia (38), opioidergic mechanisms of beneficial low-dose naltrexone action should not be ignored. Furthermore, even though fibromyalgia shares symptoms with many other multisymptom illnesses (39,40), it does not necessarily follow that low-dose naltrexone will be helpful in the other disorders. New positron emission tomography methods that target the translocator protein system on activated microglia (41–43) may provide a way of testing the validity of the microglia hypothesis.

Several other compounds have also recently been discovered to modulate microglial activity, a few examples being naloxone (44), dextromethorphan (45), 3-hydroxymorphinan (46), and ibudilast (47). These compounds have demonstrated the ability to suppress the production of proinflammatory and excitatory agents from microglia and may work via antagonism of Toll-like receptor 4 (8). While these other compounds may have a beneficial effect on fibromyalgia symptoms, we chose naltrexone because of its relatively high oral bioavailability, long history of safe use, low cost, and accessibility. Glial cell modulators represent a new approach for treating chronic diseases that may involve central inflammation. All of the above-listed compounds were designed for other purposes and were later dis-

covered to also have microglia-modulating properties. In many cases, however, the dosages needed for microglia antagonism may be much lower than those used for the original clinical purposes. Indeed, identifying a proper low dose may be critical to realizing the full neuroprotective and antiinflammatory effects of these compounds (48). The idea of keeping microglia in their quiescent, resting state is gaining traction as a target of interest (49), and we expect that new compounds for that purpose are currently in development and testing.

A limitation of this study is that the potential extended action of low-dose naltrexone renders the findings of crossover studies extremely difficult to interpret. We chose the crossover design because it allows participants to experience the drug for themselves and because statistical sensitivity can be achieved with fewer participants than in similarly powered parallel-group studies. However, bleedover effects may be prominent, especially when the placebo condition follows the medication condition. For example, a "pharmacologic conditioning" confound occurs when a prior beneficial response during a drug phase leads to heightened expectations during subsequent phases (50). We have previously observed that pain is partially suppressed from baseline levels even 1 month after stopping low-dose naltrexone. To minimize bleedover of the effects of prolonged low-dose naltrexone treatment into the placebo condition, we chose to examine only the final few days of each condition for the main analyses. While the effects of physiologic and psychological bleedover could have been further reduced with the inclusion of an interim washout period, we believed that the additional burden on the 6-month study would have increased participant attrition. We note that attrition in the study was very low. Therefore, we believe the crossover design is justified for generating preliminary data, although it will be critical to conduct larger parallel-group design studies before making recommendations for clinical practice.

Interpretation of the study results may also be hampered by the large intrinsic variability of the pain outcome variable. As seen in Figure 3, pain can fluctuate greatly, even over short periods of time. Future studies may use longer assessment periods to provide better estimates of treatment effects.

Currently, 3 treatments for fibromyalgia have been approved by the Food and Drug Administration: pregabalin (51), duloxetine (52), and milnacipran (53). Recent systematic reviews have found that all of these treatments are superior to placebo and are similar in their efficacy and tolerability (54,55). While still in the preliminary stages of investigation, we propose that low-dose naltrexone is a compound worthy of further investigation to supplement the current therapies for fibromyalgia. Our replicated observation that low-dose naltrexone affects levels of pain, together with the low cost and tolerable nature of low-dose naltrexone, makes it a promising target for future investigation.

AUTHOR 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. Younger had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Younger, Mackey.
Acquisition of data. Younger, Noor, McCue.
Analysis and interpretation of data. Younger, Mackey.

REFERENCES

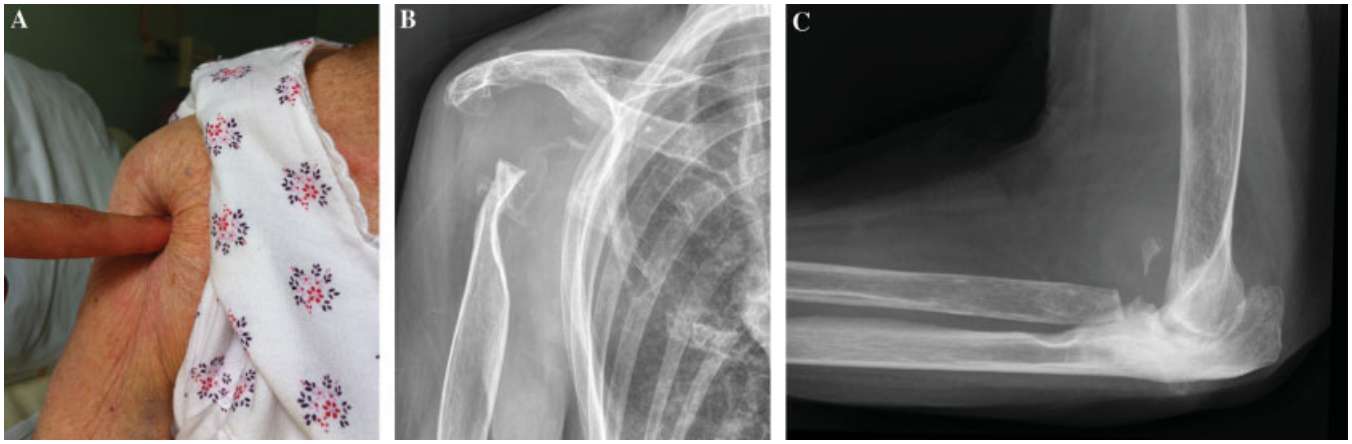
1. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. Pain Med 2009;10:663–72.
2. Smith JP, Stock H, Bingaman S, Mauger D, Rogosnitzky M, Zagon IS. Low-dose naltrexone therapy improves active Crohn's disease. Am J Gastroenterol 2007;102:820–8.
3. Smith JP, Bingaman SI, Ruggiero F, Mauger DT, Mukherjee A, McGovern CO, et al. Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn's disease: a randomized placebo-controlled trial. Dig Dis Sci 2011;56:2088–97.
4. Cree BA, Kornyeyeva E, Goodin DS. Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. Ann Neurol 2010;68:145–50.
5. Sharafaddinzadeh N, Moghtaderi A, Kashipazha D, Majdinasab N, Shalbafan B. The effect of low-dose naltrexone on quality of life of patients with multiple sclerosis: a randomized placebo-controlled trial. Mult Scler 2010;16:964–9.
6. Frech T, Novak K, Revelo MP, Murtaugh M, Markewitz B, Hatton N, et al. Low-dose naltrexone for pruritus in systemic sclerosis. Int J Rheumatol 2011;2011:804296.
7. Brown N, Panksepp J. Low-dose naltrexone for disease prevention and quality of life. Med Hypotheses 2009;72:333–7.
8. Hutchinson MR, Zhang Y, Brown K, Coats BD, Shridhar M, Sholar PW, et al. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of Toll-like receptor 4 (TLR4). Eur J Neurosci 2008;28:20–9.
9. Liu B, Du L, Hong JS. Naloxone protects rat dopaminergic neurons against inflammatory damage through inhibition of microglia activation and superoxide generation. J Pharmacol Exp Ther 2000;293:607–17.
10. Mattioli TA, Milne B, Cahill CM. Ultra-low dose naltrexone attenuates chronic morphine-induced gliosis in rats. Mol Pain 2010;6:22.
11. Lynch MA. The multifaceted profile of activated microglia. Mol Neurobiol 2009;40:139–56.
12. Watkins LR, Hutchinson MR, Ledeboer A, Wieseler-Frank J, Milligan ED, Maier SF. Glia as the "bad guys": implications for improving clinical pain control and the clinical utility of opioids. Brain Behav Immun 2007;21:131–46.
13. Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. Physiol Rev 2011:91:461–553.
14. Myers JS. Proinflammatory cytokines and sickness behavior: implications for depression and cancer-related symptoms. Oncol Nurs Forum 2008;35:802–7.
15. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The preva-

lence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28.
16. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–72.
17. Wolfe F, Clauw DJ, FitzCharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010;62:600–10.
18. Staud R. Evidence for shared pain mechanisms in osteoarthritis, low back pain, and fibromyalgia. Curr Rheumatol Rep 2011;13: 513–20.
19. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152:S2–15.
20. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18: 728–33.
21. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 1996;67:588–97.
22. Turk DC, Dworkin RH, Burke LB, Gershon R, Rothman M, Scott J, et al. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. Pain 2006;125: 208–15.
23. Arnold LM, Williams DA, Hudson JI, Martin SA, Clauw DJ, Crofford LJ, et al. Development of responder definitions for fibromyalgia clinical trials. Arthritis Rheum 2012;64:885–94.
24. Hains LE, Loram LC, Weiseler JL, Frank MG, Bloss EB, Sholar P, et al. Pain intensity and duration can be enhanced by prior challenge: initial evidence suggestive of a role of microglial priming. J Pain 2010;11:1004–14.
25. Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J Leukoc Biol 2008;84:932–9.
26. Levesque S, Taetzsch T, Lull ME, Kodavanti U, Stadler K, Wagner, A, et al. Diesel exhaust activates and primes microglia: air pollution, neuroinflammation, and regulation of dopaminergic neurotoxicity. Environ Health Perspect 2011;119:1149–55.
27. Carvey PM, Punati A, Newman MB. Progressive dopamine neuron loss in Parkinson's disease: the multiple hit hypothesis. Cell Transplant 2006;15:239–50.
28. Piche T, Gelsi E, Schneider SM, Hebuterne X, Giudicelli J, Ferrua B, et al. Fatigue is associated with high circulating leptin levels in chronic hepatitis C. Gut 2002;51;434–9.
29. Fukuda J, Nasu K, Sun B, Shang S, Kawano Y, Miyakawa I. Effects of leptin on the production of cytokines by cultured human endometrial stromal and epithelial cells. Fertil Steril 2003;80 Suppl 2:783–7.
30. White FA, Wilson NM. Chemokines as pain mediators and modulators. Curr Opin Anaesthesiol 2008;21:580–5.
31. White FA, Jung H, Miller RJ. Chemokines and the pathophysiology of neuropathic pain. Proc Natl Acad Sci U S A 2007;104: 20151–8.
32. Wang H, Moser M, Schiltenwolf M, Buchner M. Circulating cytokine levels compared to pain in patients with fibromyalgia—a prospective longitudinal study over 6 months. J Rheumatol 2008; 35:1366–70.
33. Abbadie C, Bhangoo S, De Koninck Y, Malcangio M, Melik-Parsadaniantz S, White FA. Chemokines and pain mechanisms. Brain Res Rev 2009;60:125–34.
34. Wieseler-Frank J, Maier SF, Watkins LR. Immune-to-brain communication dynamically modulates pain: physiological and pathological consequences. Brain Behav Immun 2005;19:104–11.
35. Zagon IS, Rahn KA, Turel AP, McLaughlin PJ. Endogenous opioids regulate expression of experimental autoimmune encephalomyelitis: a new paradigm for the treatment of multiple sclerosis. Exp Biol Med (Maywood) 2009;234:1383–92.
36. Narita M, Mizoguchi H, Nagase H, Suzuki T, Tseng LF. Up-regulation of spinal μ-opioid receptor function to activate G-protein by chronic naloxone treatment. Brain Res 2001;913:170–3.
37. Rajashekara V, Patel CN, Patel K, Purohit V, Yoburn BC. Chronic opioid antagonist treatment dose-dependently regulates μ-opioid receptors and trafficking proteins in vivo. Pharmacol Biochem Behav 2003;75:909–13.
38. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central μ-opioid receptor availability in fibromyalgia. J Neurosci 2007;27:10000–6.
39. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum 2007;36:339–56.
40. Yunus MB. The prevalence of fibromyalgia in other chronic pain conditions. Pain Res Treat 2012;2012:584573.
41. Thiel A, Radlinska BA, Paquette C, Sidel M, Soucy JP, Schirrmacher R, et al. The temporal dynamics of poststroke neuroinflammation: a longitudinal diffusion tensor imaging-guided PET study with 11C-PK11195 in acute subcortical stroke. J Nucl Med 2010;51:1404–12.
42. Politis M, Pavese N, Tai YF, Kiferle L, Mason SL, Brooks DJ, et al. Microglial activation in regions related to cognitive function predicts disease onset in Huntington's disease: a multimodal imaging study. Hum Brain Mapp 2011;32:258–70.
43. Gulyas B, Vas A, Toth M, Takano A, Varrone A, Cselenyi Z, et al. Age and disease related changes in the translocator protein (TSPO) system in the human brain: positron emission tomography measurements with [^{11}C]vinpocetine. NeuroImage 2011;56:1111–21.
44. Liu SL, Li YH, Shi GY, Chen YH, Huang CW, Hong JS, et al. A novel inhibitory effect of naloxone on macrophage activation and atherosclerosis formation in mice. J Am Coll Cardiol 2006;48: 1871–9.
45. Thomas DM, Kuhn DM. MK-801 and dextromethorphan block microglial activation and protect against methamphetamine-induced neurotoxicity. Brain Res 2005;1050:190–8.
46. Zhang W, Qin L, Wang T, Wei SJ, Gao HM, Liu J, et al. 3-hydroxymorphinan is neurotrophic to dopaminergic neurons and is also neuroprotective against LPS-induced neurotoxicity. FASEB J 2005;19:395–7.
47. Mizuno T, Kurotani T, Komatsu Y, Kawanokuchi J, Kato H, Mitsuma N, et al. Neuroprotective role of phosphodiesterase inhibitor ibudilast on neuronal cell death induced by activated microglia. Neuropharmacology 2004;46:404–11.
48. Chechneva OV, Mayrhofer F, Daugherty DJ, Pleasure DE, Hong JS, Deng W. Low dose dextromethorphan attenuates moderate experimental autoimmune encephalomyelitis by inhibiting NOX2 and reducing peripheral immune cells infiltration in the spinal cord. Neurobiol Dis 2011;44:63–72.
49. Ponomarev ED, Veremeyko T, Barteneva N, Krichevsky AM, Weiner HL. MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the C/EBP-α-PU.1 pathway. Nat Med 2011;17:64–70.
50. Amanzio M, Corazzini LL, Vase L, Benedetti F. A systematic review of adverse events in placebo groups of anti-migraine clinical trials. Pain 2009;146:261–9.
51. Pauer L, Winkelmann A, Arsenault P, Jespersen A, Whelan L, Atkinson G, et al, on behalf of the A0081100 Investigators. An international, randomized, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia. J Rheumatol 2011;38:2643–52.
52. Mease PJ, Russell IJ, Kajdasz DK, Wiltse CG, Detke MJ, Wohlreich MM, et al. Long-term safety, tolerability, and efficacy of duloxetine in the treatment of fibromyalgia. Semin Arthritis Rheum 2010;39:454–64.
53. Branco JC, Cherin P, Montagne A, Bouroubi A, on behalf of the Multinational Coordinator Study Group. Longterm therapeutic response to milnacipran treatment for fibromyalgia: a European 1-year extension study following a 3-month study. J Rheumatol 2011;38:1403–12.
54. Hauser W, Petzke F, Sommer C. Comparative efficacy and harms

of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain 2010;11:505–21.
55. Choy E, Marshall D, Gabriel ZL, Mitchell SA, Gylee E, Dakin HA. A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. Semin Arthritis Rheum 2011;41:335–45.e6.

DOI 10.1002/art.37774

Clinical Images: Milwaukee shoulder syndrome affecting the elbow



The patient, an 87-year-old woman, was referred to the rheumatology department for pain in the shoulders and left elbow, associated with increased markers of inflammation (C-reactive protein level 200 mg/liter). Active mobility of these joints had been severely limited for 4 months, leading to progressive incapacity of the arms. On physical examination, loss of the normal rounded contour of both shoulder muscles was apparent, with a palpable depression in the upper humeral area of the right shoulder (**A**). All of the synovial fluid cultures and blood cultures were sterile. Results of immunologic tests were negative for rheumatoid factor and anti–citrullinated peptide antibody. Radiographs showed complete bilateral osteolysis of both the humeral head and the glenoid cavity of the scapula (**B**) and severe destruction of the radial head of the left elbow (**C**), with the presence of osteochondral loose bodies. Neuropathic arthropathy was initially suspected, but careful neurologic examination, spine magnetic resonance imaging, syphilis serology tests, and electromyography did not reveal an underlying neurologic disorder such as syringomyelia (1). Posttraumatic osteolysis of the shoulder was also possible, but seemed unlikely because there had been no acute traumatic event and there was inflammatory oligoarticular involvement. Shoulder arthrocentesis yielded a hemorrhagic inflammatory fluid with no crystals seen on polarized microscopy. Alizarin red staining of the synovial fluid revealed hydroxyapatite crystals. The diagnosis of bilateral Milwaukee shoulder also affecting the left elbow was proposed, and the patient was treated successfully with a 4-week regimen of oral corticosteroids. This rare destructive arthropathy described in 1981 (2) occurs predominantly in elderly women, usually affects a single joint, and is characterized by intraarticular or periarticular hydroxyapatite crystals and rapid destruction of the rotator cuff and the glenohumeral joint (3). Calcium pyrophosphate or apatite crystal deposition involving other peripheral joints is sometimes described (1,2).

1. Ruette P, Stuyck J, Debeer P. Neuropathic arthropathy of the shoulder and elbow associated with syringomyelia: a report of 3 cases. Acta Orthop Belg 2007;73:525–9.
2. McCarty DJ, Halverson PB, Carrera GF, Brewer BJ, Kozin F. "Milwaukee shoulder"—association of microspheroids containing hydroxyapatite crystals, active collagenase, and neutral protease with rotator cuff defects. I. Clinical aspects. Arthritis Rheum 1981;24:464–73.
3. Rachow JW, Ryan LM, McCarty DJ, Halverson PC. Synovial fluid inorganic pyrophosphate concentration and nucleotide pyrophosphohydrolase activity in basic calcium phosphate deposition arthropathy and Milwaukee shoulder syndrome. Arthritis Rheum 1988; 31:408–13.

Paul Ornetti, MD, PhD
Dijon University Hospital
University of Burgundy
and INSERM U1093
Nathalie Vernier, MD
Dijon University Hospital
Clémentine Fortunet, MD
Dijon University Hospital
University of Burgundy
and INSERM U1093
Dijon, France