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A Randomized, Double-Blind, Placebo-Controlled Trial of Pramipexole, a Dopamine Agonist, in Patients With Fibromyalgia Receiving Concomitant Medications

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Objective. **To assess the efficacy and safety of pramipexole, a dopamine 3 receptor agonist, in patients with fibromyalgia.**

Methods. **In this 14-week, single-center, double-blind, placebo-controlled, parallel-group, escalating-dose trial, 60 patients with fibromyalgia were randomized 2:1 (pramipexole:placebo) to receive 4.5 mg of pramipexole or placebo orally every evening. The primary outcome was improvement in the pain score (10-cm visual analog scale [VAS]) at 14 weeks. Secondary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ), the Multidimensional Health Assessment Questionnaire (MDHAQ), the pain improvement scale, the tender point score, the 17-question Hamilton Depression Inventory (HAM-d), and the Beck Anxiety Index (BAI). Patients with comorbidities and disability were not excluded. Stable dosages of concomitant medications, including analgesics, were allowed.**

Results. **Compared with the placebo group, patients receiving pramipexole experienced gradual and more significant improvement in measures of pain, fatigue, function, and global status. At 14 weeks, the VAS pain score decreased 36% in the pramipexole arm and 9% in the placebo arm (treatment difference –1.77 cm). Forty-two percent of patients receiving pramipexole and 14% of those receiving placebo achieved ≥50% decrease in pain. Secondary outcomes favoring pramipexole over placebo included the total FIQ score (treatment difference –9.57) and the percentages of improvement in function (22% versus 0%), fatigue (29% versus 7%), and global (38% versus 3%) scores on the MDHAQ. Compared with baseline, some outcomes showed a better trend for pramipexole treatment than for placebo, but failed to reach statistical significance, including improvement in the tender point score (51% versus 36%) and decreases in the MDHAQ psychiatric score (37% versus 28%), the BAI score (39% versus 27%), and the HAM-d score (29% versus 9%). No end points showed a better trend for the placebo arm. The most common adverse events associated with pramipexole were transient anxiety and weight loss. No patient withdrew from the study because of inefficacy or an adverse event related to pramipexole.**

Conclusion. **In a subset of patients with fibromyalgia, ~50% of whom required narcotic analgesia and/or were disabled, treatment with pramipexole improved scores on assessments of pain, fatigue, function, and global status, and was safe and well-tolerated.**

Abnormal autonomic arousal (1–4), altered sleep stage architecture (5), chronic pain, and fatigue characterize fibromyalgia syndrome. The pathogenesis of fibromyalgia is a matter of debate, but centrally mediated abnormalities of sensory processing play an important role (6). Clinicians have tried various pharmacotherapies, including such agents as antidepressants, antiepileptics, muscle relaxants, antiinflammatories, sedative hypnotics, analgesics, and nutriceuticals (7). As a central neurotransmitter, dopamine influences human behavior, autonomic arousal, and sleep (8). Discovery of dopamine receptor subtypes ($D_{1–5}$) and their dopamine concentration–dependent presynaptic and postsynaptic effects has made analyses of these vital regulatory pathways more complex. These related receptors fulfill different roles in disparate locations, including D_3 receptors predominantly found in the mesolimbus (9,10).

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Dr. Holman holds patents for the use of dopamine 2/dopamine 3 receptor agonists in the treatment of fibromyalgia (patents US 6.277.875.B1 and US 6.300.365.B1).

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Adrenergic arousal arising from the locus ceruleus fragments normal sleep. Theoretically, this brainstem stimulation may be negated, or at least modulated, by adaptive neurotransmission influenced by dopamine through D_3 receptors in the mesolimbus. Dopaminergic neurotransmission reduces the expression of arousal from central sympathetic stimulation in the locus ceruleus. Consequently, a D_3 receptor agonist able to augment mesolimbic control of excessive adrenergic arousal could provide a new direction for the pharmacotherapy of fibromyalgia.

Pramipexole (Mirapex; Boehringer Ingelheim, Ridgefield, CT) is a second-generation dopamine agonist that was developed for the treatment of Parkinson's disease. It is metabolized in the renal system and does not have significant effects on the cytochrome P450 system. Thus, interactions with other medications would not be expected. However, in Parkinson's disease, 14% of patients treated with pramipexole experience hallucinations when it is used in combination with carbidopa, presumably due to enhanced D_2 neurotransmission. It has 7–10 times greater affinity for the D_3 receptor compared with the D_2 receptor and 17 times greater affinity compared with the D_4 receptor (10). It has no affinity for other dopamine receptors (D_1 or D_5) or for serotonin, acetylcholine, histamine, muscarinic, opioid, α_1-adrenergic, or β-adrenergic receptors. It has mild affinity for the α_2-adrenoreceptor, a target of clonidine and tizanidine.

Blinded, placebo-controlled studies have demonstrated its efficacy in the treatment of Parkinson's disease and restless legs syndrome (11). The cause of restless legs syndrome is unknown, but this arousal is more commonly found in patients with fibromyalgia than in healthy controls (12). Based on these observations and the encouraging results of preliminary open-label studies of pramipexole treatment of fibromyalgia (13,14), we undertook the present study to evaluate pramipexole more rigorously in a randomized, placebo-controlled trial.

PATIENTS AND METHODS

Entry criteria. Patients who were eligible for this 14-week, single-center, randomized, double-blind, placebo-controlled, parallel-group, escalating-dose trial were ages 22–67 years and fulfilled the American College of Rheumatology (ACR) 1990 criteria for the diagnosis of fibromyalgia (15). Inclusion criteria included patient-reported visual analog scale (VAS; 10-cm) scores for pain of $\geq$5 cm and tender point scores $>$10 (defined below). Exclusion criteria included uncontrolled thyroid disease, alcohol/substance abuse, pregnancy, lactation, untreated but documented sleep apnea, an Epworth Sleepiness Scale score $>$12, previous use of dopamine agonists, severe cervical pain on extension or known cervical myelopathy, and uncontrolled bipolar disorder, panic disorder, or psychosis as determined by the patient's psychiatrist.

To mimic a real-world setting, no specific medications were excluded, and a washout period was not required. Patients receiving antiepileptic, antiinflammatory, antidepressant, hypnotic, and analgesic medications, including narcotics, were eligible for enrollment if the dosages had been stable for at least 6 weeks prior to study entry and were strictly maintained throughout the duration of the study. Nonpharmacologic therapies, such as injection of trigger points, acupuncture, and massage, were allowed.

Study design. The protocol, telephone screening, and consent forms were approved by the Western Institutional Review Board (WIRB; Olympia, WA), and all patients provided written informed consent at study entry. Patients were recruited by local advertisements and preliminary telephone screenings. Purchased pramipexole tablets were processed by Olympic Pharmacy (Gig Harbor, WA) and were supplied as capsules containing 0.25 mg, 0.50 mg, 0.75 mg, and 1.0 mg; calcium carbonate placebo capsules were identical. Using computer-generated codes, Olympic Pharmacy randomly assigned packets to the placebo and active-treatment groups and maintained the security of the blind. Biweekly pill counts were performed at each study visit to monitor compliance.

Between August 2003 and February 2004, 60 patients were randomized in a 2:1 ratio of patients receiving active drug to patients receiving placebo for 14 weeks. The study medication was taken daily at bedtime and was increased weekly, as follows: 0.25 mg at week 1, 0.5 mg at week 2, 0.75 mg at week 3, 1.0 mg at week 4, 1.25 mg at week 5, 1.5 mg at week 6, 1.75 mg at week 7, 2.0 mg at week 8, 2.5 mg at week 9, 3.0 mg at week 10, 3.75 mg at week 11, and 4.5 mg at weeks 12, 13, and 14. The dosage was then tapered to 0 mg during week 15. Evaluations were conducted every 2 weeks up to week 14, and the final evaluation was performed at week 15. At the discretion of the investigator, an additional 2 weeks could be allowed to slow the dosage escalation.

Safety assessments consisted of monitoring for adverse events at each study visit and by telephone. At each study visit, orthostatic supine and standing heart rate and blood pressure (after 30 seconds to increase sensitivity to orthostasis) as well as specific gravity of the urine were assessed. Serious adverse events were reported to the WIRB, Boehringer Ingelheim, and the Food and Drug Administration. Laboratory monitoring, including levels of thyroid-stimulating hormone, aspartate aminotransferase, alanine aminotransferase, and creatinine, a complete blood cell count, and an erythrocyte sedimentation rate, were obtained at study entry and visit 8 (when patients were taking 4.5 mg every evening). Dosages of all other medications were to remain stable, but if nausea occurred, addition of a proton-pump inhibitor was allowed. All subjects were given lansoprazole, pantoprazole, esomeprazole, and rabeprazole, and then continued their preferred proton-pump inhibitor at their discretion. This strategy has been previously reported to improve pramipexole tolerability in patients with fibromyalgia (13,14).

Clinical assessments at each visit included the Fibromyalgia Impact Questionnaire (FIQ) (16), the Beck Anxiety

Index (BAI) (17), the 17-point Hamilton Depression Inventory (HAM-d) (18), the pain improvement scale, the tender point score, and the Multidimensional Health Assessment Questionnaire (MDHAQ) (19). Assessments for restless legs syndrome activity were not performed. The pain improvement scale was a self-assessment instrument to determine pain relief, and patients selected one of the following responses: none, a little, moderate, a lot, and complete relief of pain. The tender point score was defined as the sum of scores for the 18 fibromyalgia syndrome tender points, as defined by the ACR. Each tender point was scored on a scale of 0–3, where 0 = painless, 0.5 = trace tenderness, 1 = classic tenderness (~4 kg of pressure), 2 = severe tenderness with grimacing, and 3 = exquisite tenderness and sudden withdrawal (range 0–54). Both investigators standardized this tender point scoring technique to 10% variability prior to the beginning of the study, but the same assessor did not necessarily evaluate the same subject throughout the study.

Given the availability of pramipexole and the lack of industry and grant support for an open-label extension, patients were independently unblinded by Olympic Pharmacy after they completed the study in order to facilitate their appropriate medical care with their other physicians. To limit bias, the entry criteria, protocol, and study design remained strictly rigid. The investigators interacting with the patients as well as all patients still enrolled in the study remained blinded until the conclusion of the entire study.

Statistical analysis. An intent-to-treat analysis was used for all outcome measures for patients who received at least 1 dose of study drug and had at least 1 followup evaluation. The primary end point was defined as improvement in the VAS pain score on the MDHAQ from study entry to week 14 for pramipexole (dosage of 4.5 mg) compared with placebo. Secondary end points included improvements in scores on the FIQ, BAI, HAM-d, tender point assessment, pain improvement scale, and the function, psychiatric, VAS for fatigue, and VAS for global status subscales of the MDHAQ.

All computations were performed using SPSS version 10.1 software (SPSS, Chicago, IL). Data sets were initially evaluated for normality using the Kolmogorov-Smirnov test. All statistical tests were 2-sided, and P values less than 0.05 were considered significant. Normal data were evaluated by Student's t-test, with statistical significance determined after evaluation by Levene's test for equality of variances. Non–normally distributed data were evaluated by the Mann-Whitney U test. Categorical data were compared using the

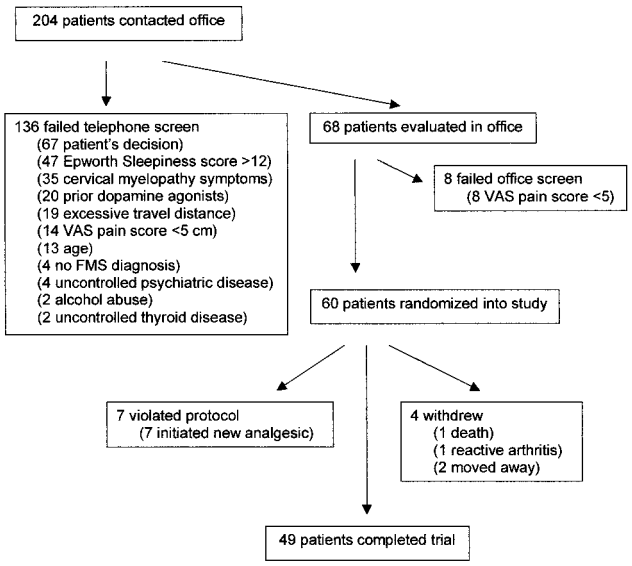

Figure 1. Flow chart showing the distribution of study patients from initial contact to completion of the study. The numbers of patients who failed the telephone screen total more than 136 because some patients had more than one of the conditions listed. VAS = visual analog scale; FMS = fibromyalgia syndrome.

Table 1. Baseline characteristics of the study patients*

	Placebo group (n = 21)	Pramipexole group (n = 39)	P
Age, mean ± SD years	46 ± 9.5	51 ± 10.1	0.10
% female	95	94	0.95
% white	95	100	0.17
Body mass index, mean ± SD	32 ± 6.6	31 ± 8.3	0.42
Duration of FMS, mean ± SD years	7.9 ± 6.8	8.9 ± 9.2	0.66
No. of previous FMS medications, mean ± SD	9.5 ± 9.1	9.7 ± 8.5	0.94
No. of previous FMS caregivers, mean ± SD	5.6 ± 4.3	5.9 ± 6.0	0.84
Education, %			0.45
<13 years	24	20	–
13–16 years	67	57	–
>16 years	9	23	–
Marital status, %			0.10
Single	19	33	–
Married	48	53	–
Divorced	28	6	–
Widowed	5	8	–
Work status, %			0.19
Working	43	55	–
Homemaker	19	14	–
Student	9	0	–
Retired	5	0	–
Disabled	24	31	–
Concomitant medications, %			
Narcotics	67	44	0.09
Antiepileptics	29	18	0.34
NSAIDs	38	36	0.87
Antidepressants†	33	44	0.44
SSRIs	52	39	0.30
RLS medications	9	5	0.57
Anxiolytics	24	18	0.59
Muscle relaxants	29	18	0.34
Hypnotics	24	15	0.43
CPAP, %	0	8	0.19

* P values were determined by Student's t-test or chi-square test for categorical data. FMS = fibromyalgia syndrome; NSAIDs = nonsteroidal antiinflammatory drugs; SSRIs = selective serotonin-reuptake inhibitors; RLS = restless legs syndrome; CPAP = continuous positive airway pressure.
† Included are generally sedating antidepressants that are taken at bedtime.

Table 2. Summary of concomitant medications*

Patient	Narcotic†	Antiepileptic	NSAID	Antidepressant	SSRI	RLS‡	Anxiolytic	Muscle relaxant	Hypnotic
1P	No	Gabapentin 300	No	No	No	No	No	No	No
2A	No	No	Ibuprofen 200	No	No	Lorazepam 1	No	No	No
3A	Tramadol 100	No	No	No	Venlafaxine 75	No	No	Cyclobenzaprine 10	No
4A	No	No	No	Trazodone 100	No	No	No	No	No
5P§	Codeine 15	No	No	No	No	No	No	No	No
6A	Hydrocodone 5	No	No	Trazodone 25	Venlafaxine 150	No	No	No	Zaleplon 10
7A§	No	No	No	Bupropion 300	Citalopram 40	No	No	No	Zolpidem 10
8P	No	No	No	Trazodone 50	Venlafaxine 75	No	No	No	No
9A§	No	No	Ibuprofen 400	No	No	No	No	No	No
10P	Methadone 15	Gabapentin 900	No	Bupropion 300	No	No	No	Methocarbamol 500	No
11A§	No	No	Naproxen 500	Amitriptyline 10	No	No	No	Methocarbamol 1,500	No
12A§	No	No	No	Trazodone 200	No	No	No	No	No
13A	Methadone 70	No	No	Trazodone 150	No	No	No	No	No
14P	No	No	No	No	Sertraline 150	No	No	No	No
15A	Tramadol	No	No	No	No	No	Diazepam 5	No	No
16A§	Propoxyphene 100	No	Valdecoxib 20	Trazodone 50	Citalopram 20	Clonazepam 2	No	No	No
17P	Hydrocodone 15	No	No	No	Paroxetine 20	No	Diazepam 5	No	No
18A	Hydrocodone 10	No	No	No	No	No	No	No	No
19A	No	No	No	No	Sertraline 50	No	No	No	No
20A	No	No	No	No	No	No	No	No	No
21P	Hydromorphone 8	Gabapentin 200	Celecoxib 200	No	No	Lorazepam 2	No	Carisoprodol 700	Zolpidem 10
22A	No	No	Naproxen 500	Trazodone 125	No	No	No	Cyclobenzaprine 10	No
23A§	No	Gabapentin 300	No	No	Fluoxetine 20	No	No	No	No
24P§	Hydrocodone 20	No	Piroxicam 20	No	Citalopram 40	No	Temazepam 15	No	Zolpidem 10
25A§	Oxycodone 20	Topiramate 100	Celecoxib 400	No	No	No	Lorazepam 2	No	No
26P	No	No	No	No	No	No	No	No	No
27P§	No	No	No	No	No	No	No	No	No
28A§	No	Gabapentin 900	Celecoxib 200	No	Citalopram 40	No	No	Carisoprodol 1,050	No
29A	Oxycodone 80	No	Ibuprofen 800	No	No	No	No	Cyclobenzaprine 10	Zolpidem 10
30A	No	No	No	Trazodone 150	Venlafaxine 150	No	Alprazolam 1	No	No

Table 2. *Cont'd*

31P	Hydrocodone 5	No	No	No	Paroxetine 20	No	No	Tizanidine 4	No
32A	No	No	No	No	No	No	No	No	No
33P	Morphine pump	No	Rofecoxib 50	No	No	No	No	No	No
34A	No	Depakote 125	No	No	No	No	No	No	No
35A	Oxycodone 10	No	Rofecoxib 50	No	No	No	Buspirone 60	Cyclobenzaprine 30	No
36P	Oxycodone 40	No	No	No	No	No	No	Cyclobenzaprine 10	Zolpidem 10
37P	Oxycodone 90	No	No	Doxepin 60	Fluoxetine 40	No	Lorazepam 2	No	No
38A	Oxycodone 20	No	Aspirin 1,000	Trazodone 150	Venlafaxine 50	No	No	No	No
39A	No	No	No	Nortriptyline 100	No	No	No	No	Zolpidem 10
40P	Hydrocodone 15	No	Diclofenac 150	Trazodone 100	Fluoxetine 20	No	No	Cyclobenzaprine 10	No
41A	No	Gabapentin 600	No	No	Fluoxetine 20	No	No	No	No
42A§	No	No	Rofecoxib 25	Trazodone 100	No	No	No	No	No
43A§	No	No	No	No	No	No	No	No	No
44A	No	No	Celecoxib 200	No	Fluoxetine 20	No	No	No	No
45P	Codeine 20	Gabapentin 1,200	Aspirin 1,000	Trazodone 50	No	No	No	No	No
46A§	No	No	No	Mirtazapine 15	No	No	No	No	No
47A	No	No	No	No	Sertraline 50	No	No	No	No
48P	Hydrocodone 10	No	Diclofenac 150	Trazodone 450	Fluoxetine 40	No	Lorazepam 1	No	No
49P	Hydrocodone 5	Gabapentin 2,700	Celecoxib 400	No	Paroxetine 20	No	Alprazolam 4	Carisoprodol 700	Zolpidem 10
50A§	Tramadol 200	No	Ibuprofen 400	Nefazodone 100	Venlafaxine 75	No	No	No	No
51A§	Codeine 10	No	Naproxen 1,000	No	No	No	No	No	No
52P	Oxycodone 20	No	No	No	Citalopram 20	Lorazepam 2	No	No	Zalepion 10
53A	Codeine 10	Gabapentin 100	No	Doxepin 10	No	No	No	Tizanidine 8	Zolpidem 10
54A§	Hydrocodone 5	No	No	Nefazodone 100	Paroxetine 20	No	No	No	No
55A	No	Gabapentin 600	No	No	No	No	No	No	No
56A	Oxycodone 240	No	No	No	No	No	Alprazolam 1	No	No
57P	No	No	No	No	No	No	No	No	No
58A§	Hydrocodone 10	No	No	No	No	No	Clonazepam 1	No	No
59A§	Morphine 150	No	No	Trazodone 100	Citalopram 20	No	Clonazepam 3	No	Zolpidem 10
60P	No	Gabapentin 300	Naproxen 500	Amitriptyline 10	Citalopram 20	No	No	No	No

* Dosages of medications represent milligrams in 24 hours. Patient numbers are followed by the randomization abbreviation (A = active-treatment arm; P = placebo arm).
† Non-narcotic analgesics such as tramadol were included in this category.
‡ Medications considered for this category included those used for restless legs syndrome (RLS) that are taken exclusively at bedtime (clonazepam, lorazepam, and carbidopa).
§ Patient experienced a ≥50% decrease in pain score (by visual analog scale) measured at study end.

chi-square test, and safety data were evaluated by Fisher's exact test. Correlations were assessed by Pearson's correlation coefficient, if parametric, or by Kendall's tau, if nonparametric due to small data sets. In a secondary analysis, the influence of demographic data on outcome was analyzed using analysis of covariance (ANCOVA).

RESULTS

Characteristics of the study patients. In response to newspaper advertisements, 204 patients contacted the investigators to inquire about the study and were screened by telephone. Sixty-eight of these patients were evaluated in the clinic, and 60 of them were entered into the study. Reasons for lack of participation were as follows: patient's decision (33%), Epworth Sleepiness Scale score >12 (23%), cervical spine myelopathy symptoms (17%), VAS score for pain <5 cm (11%), previous use of dopamine agonists (10%), excessive travel distance (9%), age (6%), uncontrolled psychiatric disease (2%), lack of fibromyalgia diagnosis (2%), heavy alcohol use (1%), and uncontrolled thyroid disease (1%) (Figure 1).

Baseline characteristics of the study patients are summarized (Table 1). Three men and 57 women were enrolled into the study. Their mean age was 49 years (range 22–67 years), their self-reported mean duration of fibromyalgia syndrome was 8.6 years (range 1–50 years), and they had taken a mean of 9.6 medications for fibromyalgia syndrome (range 1–40), which were prescribed by a mean of 5.8 medical professionals (range 1–30). Preexisting renal disease and orthostasis were not exclusion criteria, but none of the subjects had either disorder at study entry. A greater percentage of patients in the placebo arm used narcotic analgesics, but the treatment groups were well matched overall, and there were no statistically significant differences between the 2 groups. A summary of concomitant medications taken by the study patients is shown in Table 2.

Of the 39 patients randomized to receive pramipexole, 33 (85%) completed the study. One withdrew immediately after the entry visit because of lack of interest and an impending job transfer. Of the 21 patients randomized to receive placebo, 16 (76%) completed the study. One withdrew at week 3 for the new occurrence of reactive arthritis, 1 moved to Central America at week 10, and 1 died at week 10 of unrelated medical issues. Protocol violations for initiating a new medication occurred in 2 patients in the placebo arm and 5 in the active arm; medications begun were citalopram (week 3; pramipexole), tramadol (week 5; pramipexole), methadone (week 5; pramipexole), gabapentin (week 7; placebo), valproate (week 7; pramipexole), diazepam (week 9; pramipexole), and zalepion (week 12; placebo).

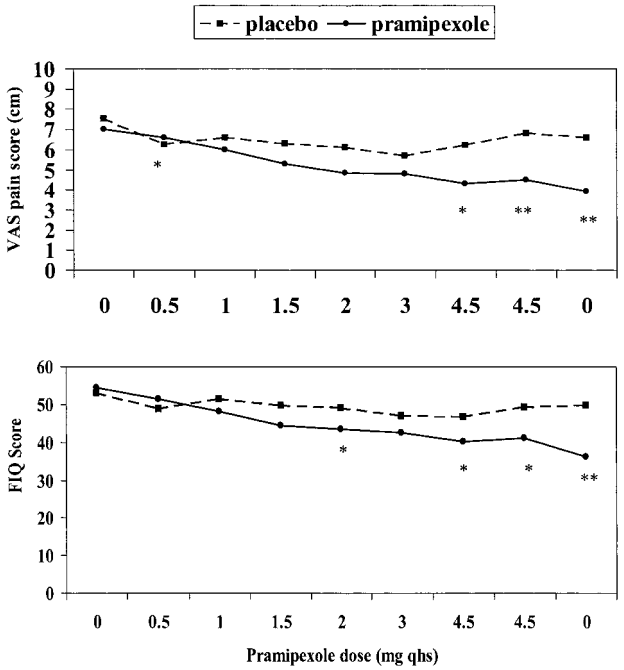

Figure 2. Change in pain scores (10-cm visual analog scale [VAS]) and Fibromyalgia Impact Questionnaire (FIQ) scores in the pramipexole and the placebo groups over 14 weeks. * = $P < 0.05$; ** = $P < 0.01$ for the relative difference between pramipexole and placebo, by 2-tailed *t*-test.

Given the potentially beneficial effects of these new medications, efficacy assessments were made using only data obtained prior to the violation, but the patients continued in the study to monitor safety. No one withdrew because of inefficacy or a pramipexole-related adverse event.

Efficacy. The pramipexole group noted significantly decreased pain compared with the placebo group at study end (week 14; 4.5 mg), as determined by scores on the VAS (Figure 2). The mean ± SEM decrease in the VAS score for pain from baseline to the study end point was –2.48 ± 0.38 cm (36%) in the pramipexole group and –0.71 ± 0.54 cm (9.4%) in the placebo group, with a between-group difference of –1.77 cm (95% confidence interval [95% CI] –3.07, –0.47) ($P = 0.008$) (Table 3). Significant improvement was also noted at week 12 (dosage of 4.5 mg) ($P = 0.03$) and at week 15 following the 1-week taper, with a difference of –2.36 cm (95% CI –3.79, –0.86) ($P = 0.003$). Except at week 3, all other VAS assessments for pain trended better for the

Table 3. Results of the MDHAQ, FIQ, HAM-d, BAI, and tender point score outcome measures at study end*

	Placebo group		Pramipexole group		Between-group difference at end point (95% CI)	*P*
	No. of patients	Change, mean ± SEM	No. of patients	Change, mean ± SEM		
MDHAQ subscale scores, range 0–10						
Pain	21	−0.71 ± 0.54	38	−2.48 ± 0.38	−1.77 (−3.07, −0.47)	0.008
Fatigue	21	−0.55 ± 0.46	38	−2.11 ± 0.48	−1.56 (−2.88, −0.24)	0.021
Global status	21	−0.16 ± 0.61	38	−2.52 ± 0.43	−2.35 (−3.82, −0.89)	0.002
Function	21	0.01 ± 0.39	38	−0.83 ± 0.21	−0.84 (−1.64, −0.04)	0.041
Psychiatric	21	−1.47 ± 0.46	38	−1.92 ± 0.43	−0.51 (−1.85, 0.82)	0.44
FIQ total score, range 0–80	21	−3.73 ± 2.79	38	−13.30 ± 2.75	−9.57 (−18.01, −1.05)	0.028
HAM-d total score, range 0–52	21	−1.33 ± 2.14	38	−4.84 ± 1.69	−3.51 (−9.07, 2.05)	0.24
BAI total score, range 0–63	21	−4.38 ± 1.68	38	−7.00 ± 1.67	−2.62 (−7.77, 2.53)	0.31
Tender point score, range 0–54	21	−9.55 ± 1.92	38	−14.58 ± 2.16	−5.03 (−11.52, 1.46)	0.13

* MDHAQ = Multidimensional Health Assessment Questionnaire; FIQ = Fibromyalgia Impact Questionnaire; HAM-d = Hamilton Depression Inventory; BAI = Beck Anxiety Index.

pramipexole arm without achieving statistical significance. Post hoc analysis of VAS scores for pain demonstrated that 82% of the patients taking pramipexole noted some improvement compared with 57% of those taking placebo ($P = 0.04$). A ≥50% decrease in pain was achieved by 42% of those taking pramipexole compared with 14% of those taking placebo ($P = 0.03$)

Secondary measures of efficacy favoring pramipexole over placebo included the FIQ score (Figure 2), pain improvement scale (Figure 3), and the MDHAQ function, VAS fatigue, and VAS global scores (Table 3). At week 14 (dosage of 4.5 mg), the total FIQ score decreased by a mean ± SEM of –13.30 ± 2.75 (24%) in the pramipexole group and –3.73 ± 2.79 (7%) in the placebo group, with a between group difference of –9.57 (95% CI –18.01, –1.05) ($P = 0.028$). Following the taper at week 15, the between-group difference was –14.1 (95% CI –23.0, –5.17) ($P = 0.003$). The FIQ scores also improved significantly at week 8 (dosage of 2.0 mg; $P = 0.047$) and week 12 (dosage of 4.5 mg; $P = 0.047$). Positive trends for the HAM-d total score, the BAI total score, the tender point score, and the MDHAQ psychiatric score were evident, but they did not reach statistical significance. Subjects with abnormal HAM-d and BAI scores at study entry did not demonstrate a more substantial trend toward improvement with pramipexole.

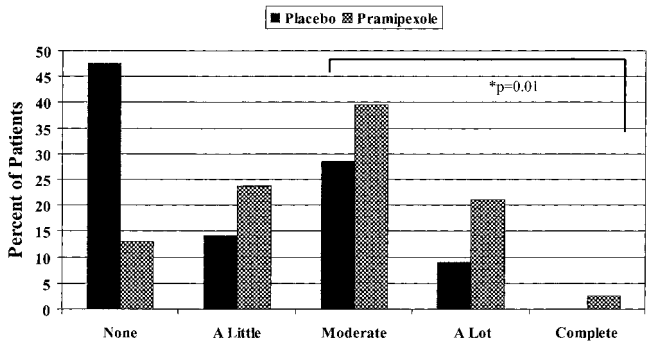

Figure 3. Patients' assessments of improvement in pain from baseline to study end (week 14), by treatment group. Significantly more patients in the pramipexole group experienced moderate or better improvement compared with those in the placebo group, by chi-square test.

ANCOVA revealed that all demographic variables and concomitant medication categories, including narcotic use ($F = 0.002$, $P = 0.96$), education level ($F = 0.094$, $P = 0.76$), or disability status ($F = 0.32$, $P = 0.57$), did not significantly influence the VAS pain score outcome or the occurrence of adverse events.

Safety. Of the 59 patients who had at least 1 dose of study medication, 100% of them experienced at least 1 adverse event (Table 4). Most statistically significant adverse events included weight loss (mean –3.3 lbs; range of changes in weight –24 to +15 lbs) and increased anxiety in the pramipexole group and weight gain (mean 4.7 lbs; range of changes in weight –7 to +19) in the placebo group. Pramipexole was well tolerated, although nausea was very common in both treatment groups. Response to the voluntary addition of proton-pump inhibitors to treat the nausea was similar for both groups (62% in the placebo group versus 71% in the pramipexole group), and the proton-pump inhibitor response and patient preference were not predictable, as previously described (14). Patient preferences in the placebo group versus the pramipexole group for lansoprazole 30–90 mg (15% versus 20%), pantoprazole 40–120 mg (39% versus 23%), esomeprazole 40–120 mg (31% versus 31%), and rabeprazole 20–60 mg (15%

Table 4. Adverse events observed in at least 5% of patients*

Adverse event	Placebo group (n = 21)	Pramipexole group (n = 38)	*P*
Nausea	71	79	0.83
Weight loss (>5 lbs)	10	40	0.01
Infection	24	37	0.23
Weight gain (>5 lbs)	57	21	0.01
Increased anxiety	0	18	0.04
Diarrhea	0	17	0.06
Morning somnolence	0	16	0.06
Dizziness	19	13	0.84
Vomiting	0	13	0.10
Constipation	10	13	0.56
Headache	19	13	0.84
Increased insomnia	19	11	0.90
Diaphoresis	5	11	0.41
Tachycardia	0	8	0.26
Decreased memory	5	8	0.55
Bloating	0	5	0.41
Injury	5	3	0.88
Muscle spasm	5	3	0.88
Urinary frequency	10	3	0.29
Urticaria	5	3	0.88
Edema	10	3	0.29
Hiccough	5	0	0.36
Tinnitus	5	0	0.36
Chest pain	5	0	0.36

* Values are percentages of patients. *P* values were calculated by Fisher's exact test.

versus 26%), respectively, were not statistically significantly different. For 1 patient in the study, the dosage escalation was delayed for 1 week because of nausea (pramipexole group). In contrast to the treatment of Parkinson's disease with pramipexole, hallucinations and sleep attacks were noticeably absent in our study patients. Infections were common, but were equally distributed between the 2 study groups.

Results of tests for hematopoietic, hepatic, renal, and thyroid function and inflammation were uniformly normal at study entry and at the final evaluation. Orthostatic hypotension, defined as a decrease in systolic blood pressure of 10 mm Hg combined with an increase in heart rate of 20 beats per minute, as assessed in both the supine and the standing positions, was not found at any visit.

The incidence of serious adverse events was 2.6% in the pramipexole group and 4.7% in the placebo group. One patient died during the study; the cause of death was unclear but was thought to be unrelated to participation in the placebo arm of the study. One serious adverse event occurred in the pramipexole group. A patient was hospitalized because of transient global amnesia that lasted <24 hours. Despite a detailed evaluation, the cause remained obscure and did not recur. Investigators were informed of these events 1 week after the adverse event had resolved, and the patient elected to continue study participation. The study drug was continued (double-blinded), and the patient successfully completed the study 6 weeks later.

DISCUSSION

In this randomized, double-blind trial, pramipexole demonstrated greater efficacy compared with placebo on measures of pain, function, fatigue, and global status after a 14-week, fixed escalation of the dosage to 4.5 mg taken at bedtime. This is the first trial of pramipexole and only the second trial for a D_3 receptor agonist in the treatment of fibromyalgia (20).

Pramipexole was generally well tolerated. These patients did not have the sleep attacks or hallucinations commonly described by patients taking pramipexole at a dosage of up to 1.5 mg orally 3 times a day for the treatment of Parkinson's disease. Orthostatic hypotension was not seen at any treatment visits. About 40% of patients in the pramipexole arm lost 1–24 pounds over 14 weeks. During the study, weight loss was unpredictable and random among the subjects, with wide variability. Consequently, significant weight fluctuations were not noticed by the investigators or typically noted by the patients. A mean loss of 3.3 lbs of weight in the pramipexole group over 14 weeks was interesting, but was too small to affect the double-blinded study design. Mild weight gain was more common in the placebo arm.

Patients did not appear to lose weight because fibromyalgia symptoms improved. Weight loss in our study patients did not correlate with pain response or improvement in fatigue, function, or HAM-d scores. The impact of D_2 receptor inhibition on weight gain in patients taking antipsychotic medications has suggested a role for a dopaminergic influence on the metabolic rate (21), but the role of D_3 is unknown.

In both arms of the study, reports of nausea were remarkably common. An emphasis of the language in the consent form on the potential for nausea and discussions of proton-pump inhibitor dosing to control the nausea may have influenced the incidence of this adverse event. It is possible that some subjects may have erroneously suspected that they were receiving the active drug if they developed nausea. While nausea and medication intolerance are common for patients with fibromyalgia, it is unclear whether this may have affected the placebo response during the study.

Increased anxiety was noted by 18 of 38 subjects

who took pramipexole and by none who took placebo ($P = 0.04$). In contrast, the change in BAI scores from baseline reflected only a modest improvement in the pramipexole group as compared with the placebo group ($P = 0.31$) (between group difference –2.62 [95% CI –7.73, 2.53]). This may be explained by the fact that cumulative adverse event reporting describes transient episodes of anxiety that are possibly related to a paradoxical stimulatory event rather than chronic anxiety. Interestingly, anxiety was usually reported early in the pramipexole dosage titration (<2.0 mg every evening), as has previously been described (13).

Most trials do not report outcome measures after discontinuation of an investigational medication. We chose to report these data to further explore safety and to measure rebound symptoms of fibromyalgia. The VAS scores for pain and the FIQ scores decreased further at the conclusion of the 7-day taper period. Scores in the placebo group did not change. This study was not designed to address this finding or record additional data, but the finding raises interesting questions about a mechanism of action of pramipexole in patients with fibromyalgia.

Dopaminergic neurons in the mesolimbus decrease tonic pain in animal models (22). Dopamine and D_2 agonists can decrease *N*-methyl-D-aspartate (NMDA)–mediated pain through activation of a receptor tyrosine kinase (23). Yunus (24) has proposed that dopamine agonists act as analgesics, but they may also play a more complex role, possibly a central autonomic regulatory role. Its relatively short serum half-life (8 hours) and efficacy when taken at bedtime would not favor a purely analgesic explanation for the effects of pramipexole. A dynamic neuroregulatory role deserves further study.

Although the pathogenesis of fibromyalgia is unclear, Wood (25) has suggested a central role for dopamine and the hippocampus, which mitigates memory, learning, stress modulation, and nociception. The hippocampus also inhibits adrenergic arousal arising from the locus ceruleus (26). Chronic pain states alter hypothalamic–pituitary–adrenal axis activity and induce hippocampal atrophy (27). Consequently, modulation of adrenergic arousal could be impaired.

Inappropriate arousal of the sympathetic nervous system has also been demonstrated in fibromyalgia syndrome (28). But, autonomic tone depends on homeostatic balance. Inhibitory dopaminergic neurotransmission in the hippocampus counteracts stimulatory arousal from the locus ceruleus. Excessive arousal or inadequate mesolimbic attenuation of adrenergic arousal, or both, could fragment sleep stage architecture in patients with fibromyalgia. The specificity of pramipexole for the D_3 receptor favors a hippocampal effect, because D_3 receptors are found in the mesolimbic hippocampus and not in the locus ceruleus (29).

Dopamine-mediated D_3 effects in the mesolimbus are concentration-dependent, and a 4.5-mg dose of pramipexole every evening would be considered high compared with the lower doses typically used to treat restless legs syndrome or Parkinson's disease. High concentrations of pramipexole favor postsynaptic neurotransmission (10). Lower concentrations favor a presynaptic effect that inhibits dopaminergic neurotransmission in the hippocampus. Increased anxiety noted in patients taking pramipexole tended to occur very early in the dosage escalation. We hypothesize that lower pramipexole doses induced anxiety (adrenergic arousal) by initially enhancing presynaptic neurotransmission in the hippocampus. This action would favor an initial decrease in hippocampal activity and reduce its normal attenuation of adrenergic arousal. Gradually increasing the pramipexole dosage sufficiently enhances its postsynaptic effect. Consequently, this increasing postsynaptic dopaminergic neurotransmission would promote and augment hippocampal control of excessive adrenergic arousal. Future studies could quantify these proposed autonomic effects and their impact on sleep stage architecture with different dosages of pramipexole.

While autonomic dysregulation has been demonstrated in fibromyalgia, the role of autonomic imbalance in the pathogenesis of fibromyalgia remains unclear. Moldofsky and colleagues (5) induced fibromyalgia symptoms in normal subjects by using an auditory arousal to disrupt deep, non–rapid eye movement, stage 3/4 sleep for 4 consecutive nights. In a study of middle-aged women conducted in 1999, Lentz and colleagues (30) reproduced Moldofsky's findings; however, in a 1998 study, Older and colleagues (31) did not produce fibromyalgia symptoms despite effective reduction of stage 3/4 sleep. However, Older et al used a different arousal technique for fragmenting deep sleep stages. Their choice of music rather than a startling, computer-generated sound may indicate that the nature of the arousal matters as much as the actual disruption of sleep. Polysomnographic studies of pramipexole taken at bedtime in the dosages we used to treat fibromyalgia syndrome are needed to document whether its therapeutic effect occurs by abrogating the aberrant sympathetic arousal that fragments deep sleep.

These observations have led to the hypothesis that dysautonomic regulation drives the symptoms of many disorders commonly seen in patients with fibro-

myalgia (32), including irritable bowel syndrome, gastric hyperacidity, irritable bladder, anxiety disorders, palpitations, and temperature dysregulation. Fragmented sleep and loss of normal deep-sleep stages may simply be another consequence of prolonged dysautonomic arousal. It will require further study to determine whether fibromyalgia is the predictable sequela of abnormal sleep or the resultant complex of inadequate stage 4 sleep combined with its dysautonomic protagonist.

This study has a variety of limitations and unorthodox design features. First, most fibromyalgia clinical trials do not allow concomitant medications. While data from previous trials may be more readily interpretable, patients who are willing to participate in such trials may not represent the norm. Although no medication has yet been approved specifically for the treatment of fibromyalgia, most patients have found some medications to be partially beneficial. Many are unwilling to discontinue their medications to participate in a typical clinical trial including these subjects. In clinical practice, caregivers often assess new medications as an augmentation strategy similar to this study design.

Our inclusion of patients taking stable dosages of other medications for fibromyalgia also increased the risk of Type II error. Monitoring patient commitment to stable dosages of medications was critical to assessing the treatment response. Initiating any potentially beneficial medication during the study could artificially affect the results of response analysis. Consequently, for protocol violations, the response at the final, untainted, pramipexole dosage was used as the final response. This approach reduced this confounding variable, but it also decreased the final treatment response over baseline as compared with placebo.

This protocol may be more applicable to a subset of patients with partially treated or possibly more severe fibromyalgia. But, the study design limits the interpretation of why or how pramipexole may improve pain, fatigue, and function scores. Also, while ANCOVA did not demonstrate a significant influence of demographic variables on treatment outcome, the study was not sufficiently powered to predict which combination of concomitant medications might yield a positive response to this adjunctive use of pramipexole. Longer trials are required to confirm these results, particularly in subjects who have discontinued concomitant medications.

The optimal rate of dosage escalation and the impact of other dosing schemes were not addressed in this study. However, the gradual increase in pramipexole dosage over many weeks appears central to the success of the protocol. Other limitations include the 14-week duration of the study. These efficacy and safety results may not be generalizable to a longer duration of treatment. Since pharmacokinetic data are not available for treatment of humans with 4.5 mg of pramipexole each evening, accurate dopamine receptor dynamics and other potential pramipexole-related effects are unknown.

Finally, it should be noted that some exclusion criteria in this study were particularly important. Both positional cervical myelopathy (33) and untreated obstructive sleep apnea (34) are potent adrenergic arousals that commonly contribute to autonomic dysregulation. Both conditions limit the efficacy and tolerability of a D_3 agonist (13) when used to treat fibromyalgia. Given the significant prevalence of cervical pain and obstructive sleep apnea in patients with fibromyalgia, many may not respond to treatment with pramipexole. Although cervical pain on extension may result from a variety of causes, it was thought to be a reasonable query with which to exclude positional cervical myelopathy. Future studies may clarify why and how these two complex arousals influence sleep stage fragmentation, pain, fibromyalgia, and treatment response to a dopamine agonist.

In summary, a new treatment approach using a D_3 receptor agonist offers hope to patients with fibromyalgia. This 14-week study of pramipexole in patients with fibromyalgia demonstrated improvement in measures of pain, fatigue, function, and global status, with a reassuring adverse event profile. Further investigation of this pramipexole treatment paradigm is warranted to determine its mechanism of action in patients with fibromyalgia, its long-term risks and benefits, and to confirm these findings in patients not taking concomitant medications.

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