PAIN

fibromyalgia symptoms in comorbid patients

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Response letter.
Manuscript entitled: Visceral pain as a triggering factor for fibromyalgia symptoms in comorbid patients, by Costantini et al

We thank both reviewers for their constructive criticism to the manuscript. We have addressed all the points raised in their report, as detailed below. All the changes performed are highlighted in yellow in the text.

Reviewer #1: This is an interesting and well-written paper from an experienced group. They have compared patients with fibromyalgia alone with those with comorbidity with IBS, primary dysmenorrhea and dysmenorrhea secondary to endometriosis and finally with diverticulosis. They demonstrate that all comorbid groups have significantly higher fibromyalgia related pain and also hyper analgesia after deep tissue. Visceral pain also correlated inversely with muscle pain thresholds at all sites. Furthermore, treatment of co-morbid conditions improve fibromyalgia associated pain. They conclude that visceral pain enhances fibromyalgia probably by augmenting the level of central sensitisation.

Overall this is a well conducted study but there are some methodological issues that need clarification.

Q: 1. It is worth clarifying whether all sub-groups of fibromyalgia were recruited from only one department or were they recruited from different departments such as gastroenterology and gynaecology etc.

A: *All patients of the study were recruited from only one center (Fibromyalgia Center at the Department of Medicine and Science of Aging), although they had been referred to the center by various physicians/specialists (including gastroenterologists and gynecologists). This has now been clarified in the text.*

Q: 2. Were successive patients recruited between January 2006 to December 2007? If not then how were the patients chosen for this study. The author should provide a breakdown of how many patients were assessed for each sub-group, how many met the inclusion criteria, what was the drop-out rate etc. They can provide this information in the supplementary material. This is important otherwise selection bias can be an issue.

A: *We thank the reviewer for raising this important point which we realize had been not sufficiently detailed in the manuscript. We have now provided all the requested pieces of information in the supplementary material (Table 1).*

Q: 3. How did the authors ensure that no other medical therapy was started in the comorbid sub group such as increasing dose of amitriptyline or starting of another medicine that may have contributed to a change in their symptoms? Was a specific examination of their medical records performed to ensure that this is not the case? In addition, psychological therapy can also significantly improve symptoms and did the authors ensure that the patients had not been referred for any psychological therapy such as cognitive behavioural therapy etc. in their follow up period.

A: *During the study period (up to 2 years for each patient) patients were monitored through regular control visits at the center (every 6 months), and monthly phone calls by the study personnel to assess adherence to the protocol and make sure that no other therapy, either medical, or psychological, had been initiated which could have contributed to the results of the study independently of the therapy for the comorbidity that was under assessment. This has now been specified in the text.*

Q: 4. In the statistical analysis how did the authors determine whether their data was normally distributed or not because when using a Student T test it is important to ensure normal distribution of data through tests such as Shapiro-Wilk test etc.

A: *Thank you for bringing up this important methodological issue for the statistical analysis. After consultation with our reference statistician and application of the Shapiro-Wilk test to all data, normal distribution was ascertained for the majority of the analyzed variables and therefore the analysis with 1-way ANOVA and Student's t-test was maintained. In a few cases of nonnormal distribution, nonparametric tests were instead applied: Kruskal-Wallis Test and Wilcoxon matched-pairs signed-ranks test, which confirmed the results and their significance (only slight changes in the level of significance occurred in some instances, highlighted in yellow in the text). This has now been specified in the manuscript.*

Q: 5 Recently comorbidity with hypermobile Ehlers-Danlos Syndrome has been described. This condition can be associated with all the comorbidities that the authors describe. i.e. fibromyalgia or chronic wide spread pain, IBS and dysmenorrhea etc. The authors do not seem to have studied patients for this overlap, however it would be useful to include a mention of this overarching comorbidity in their discussion section because the EDS hypothesis suggests that the comorbidities are due to a common heritable disorder of connective tissue.

A: *This is a very interesting point. We have introduced this concept in the discussion, as suggested, quoting relevant recent papers with this respect.*

Minor Points:
Q: * I would suggest that the authors use a term other than "centrally routed

syndrome" in their abstract and introduction. The term central sensitisation would be more appropriate here.

A: *The expression "centrally routed syndrome" has been replaced with "central sensitization" in both abstract and introduction.*

Q: * The authors do not have to repeat the inclusion criteria for fibromyalgia for all the comorbid groups. They should just have one description of the fibromyalgia inclusion at the beginning of the inclusion criteria and then they should just state that this criteria was used for all the sub groups.

A: *The inclusion criteria for all the subgroups have been summarized, as requested.*

Reviewer #2: PAIN-D-17-00393
To the authors:
This is a nicely done study of the contribution of co-morbid visceral pain conditions to the pain of FMS. The authors have not only shown than there is an association between the level of pain or the activity of co-morbid visceral pain, but have shown that successful treatment of visceral pain conditions reduces FMS pain. The authors conclude, based on the evidence from their studies, that visceral pain can be a triggering factor that increases or augments the clinical symptoms of FMS, specifically that of pain or hyperalgesia. and that the mechanism is most likely mediated through central nervous system sensitization.

Q: I have one or two questions. In the discussion the authors comment on the reduction of FMS symptoms with treatment, but in reality, they only looked at pain and hyperalgesia. They looked at flares of FMS and of drug usage, perhaps as surrogate markers of FMS activity, but did not look at specific issues such as sleep, fatigue, headache, etc. I do not disagree with the author's conclusions, but suggest that they clearly state that they can say that the overall number of FMS flares is reduced but they cannot say that sleep, fatigue, and other non-measured aspects of FMS were specifically altered, although there was an overall reduction in FMS flares. If the authors have more information about the somatic symptoms of FMS and how they were affected by treatment of visceral pain, that should be mentioned.

A: *We fully acknowledge the importance of the issue raised by the reviewer. Unfortunately we did not look systematically at the other mentioned symptoms in relation to the present protocol, therefore we are not able to say if treatment of the visceral comorbidities also had an impact on these symptoms.*
As suggested, we have now clearly stated in the Discussion that the effects we observed were specifically on musculoskeletal FMS pain, not including other symptoms, which will certainly need to be evaluated in future studies on comorbitities in FMS.

Q: The authors emphasize the effect of co-morbid visceral painful conditions on central sensitization. Do the authors exclude an effect of peripheral sensitization as an additional factor playing a role? It would seem so, as they mention that the visceral co-morbidities can trigger FMS symptoms, but if they consider peripheral sensitization to be a factor, it should be mentioned along with central sensitization.

A: *Peripehral sensitization from the affected visceral organs can, indeed, be an important factor, especially as most of the considered comorbidities are in fact characterized by peripheral sensitization at visceral level. We have now reported this concept in the discussion*.

Q: Finally, in discussing mechanisms, the authors do not mention alteration of central pain modulation as a possible mechanism. It would seem that treatment of visceral pain co-morbidities might restore normal central pain modulation mechanisms as well as affect central sensitization.

A: *This is another important point, we have now included this possibility in the discussion section, as suggested.*

Q:The points that I raise are rather minor points, but the authors should consider whether a mention of these possible mechanisms along with central sensitization would broaden the consideration of where visceral pain impacts pain transduction and transmission in the peripheral and central nervous system in a chronic widespread pain syndrome such as fibromyalgia.

A: *We are gratetul to the reviewer for raising these crucial pathophysiological issues. We believe that their inclusion in the discussion renders it more complete and provides a better interpretation of data.*

Q: The paper is clearly written. The abstract and introduction are well presented. The methods section is clear. The discussion is very good with the caveat to consider my comments above, which should not be taken in any way to diminish the overall completeness and appropriateness of the discussion section, and the figures are clear and sufficient. The references are also appropriate and adequate.
A: *Thank you!*

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Keywords: fibromyalgia syndrome; visceral pain; IBS; dysmenorrhea; endometriosis; diverticulitis; hyperalgesia; treatment; comorbidity; chronic overlapping pain conditions

Visceral pain as a triggering factor for fibromyalgia symptoms in comorbid patients

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1. Introduction

Fibromyalgia syndrome (FMS) is a chronic widespread pain condition associated with sleep disorders, physical exhaustion and affective dysfunction [30]. Its prevalence estimates range from 2 to 6% of the general population, with a net female predominance (13.7-2.3/1) [33]. The 1990 FMS diagnostic criteria of the American College of Rheumatology (ACR) [51] require fulfilment of 2 conditions: (1) diffuse musculoskeletal pain for at least 3 months; and (2) positivity of at least 11 of 18 predetermined body sites called tender points (TePs), i.e., exquisite tenderness with a standard pressure of 4kg [20]. The most recently proposed criteria no longer require TePs evaluation while considering other clinical variables related to the frequent FMS comorbidities (e.g., visceral pain, headache, sleep and mood disorders) [50]. These new criteria being less restrictive, an ACR 1990 diagnosis of FMS is normally confirmed with their application [3]. The pathophysiology of fibromyalgia remains to be investigated in full; however, a definite role has been established, in genetically predisposed individuals, for central sensitization processes, whereby pain signals are amplified due to an imbalance of neurotransmitters involved in nociceptive transmission or its control in the Central Nervous System (CNS) [1,2,7,11,12,35,42]. The clinical correlate of central sensitization in the syndrome is represented by the lowered pain threshold to different stimuli in superficial and deep somatic tissues (skin, subcutis and muscle) which is generalized and not only confined to painful zones [3,23,47]. Although FMS is mainly regarded as a central sensitization syndrome, the importance of peripheral/additional nociceptive factors in

triggering/maintaining its symptoms has been increasingly recognized in recent years [22]. Several studies have, in fact, documented that coexisting localized somatic pain sources, e.g., myofascial trigger points or painful joints, can enhance FMS symptoms, and their local treatments also improve FMS pain and tenderness [3,23]. Similarly, the co-occurrence of an additional pain condition like migraine, increases FMS pain [25]. In the visceral pain domain, a previous study in FMS patients with gallbladder calculosis also showed that biliary colics worsen FMS symptoms, with long-term improvement of the latter after laparoscopic gallbladder removal [13]. FMS is highly comorbid with several visceral pain disorders, such as Irritable Bowel Syndrome (IBS), dysmenorrhea, endometriosis, and abdominal pain of various origin [8,34,39,45,52]. Although clinical observations indicate that painful episodes from these disorders may worsen the typical FMS pain, to date no systematic studies have been conducted with this respect. The first objective of this study was therefore to assess if FMS patients with abdominal/pelvic pain from a visceral comorbidity including IBS, diverticulitis, dysmenorrhea or endometriosis presented more FMS symptoms - spontaneous musculoskeletal pain and somatic hypersensitivity - than those with FMS only, and if a correlation could be established between the extent of visceral pain and that of FMS. The second objective was to verify if a specific, effective therapy of the visceral condition vs no therapy, also had an impact on FMS, particularly in improving FMS pain and decreasing drug consumption for its control, as well as in decreasing the level of generalized somatic hyperalgesia.

2. Materials and Methods

2.1. Patients

Female patients affected with fibromyalgia syndrome were considered, without and with concurrent visceral pain conditions, all outpatients of the Fibromyalgia Center at the Department of Medicine and Science of Aging of the "G. D'Annunzio" University of Chieti (Suppl. Table 1 for recruitment period/criteria). The FMS diagnosis had been primarily performed according to the ACR criteria (1990) with confirmation of the diagnosis according to the 2010 revised preliminary criteria (based on a retrospective analysis of data present in the patients' records at the first visit, regarding site/distribution of FMS pain areas and the presence of comorbidities) [50,51]. In particular, five groups of FMS patients were considered, with: (1) no additional pain conditions (FMS); (2) concurrent Irritable Bowel Syndrome (FMS+IBS); (3) concurrent primary dysmenorrhea (FMS+Dys); (4) concurrent dysmenorrhea secondary to endometriosis (FMS+Endo); (5) concurrent sigmoid colon diverticulosis, with recurrent episodes of diverticulitis (FMS+Div).

The protocol adhered to the principles expressed in the Declaration of Helsinki and received ethic approval by the Institutional Review Board of the Department of Medicine and Science of Aging – of the "G. D'Annunzio" University of Chieti (5/1,03.31.2003). A written informed consent was obtained from all patients (see inclusion criteria).

2.2. Inclusion criteria

Inclusion criteria for all groups were: female sex, age 18-45 years; a diagnosis of FMS performed by a specialist 2-5 years before, with the start of symptoms not earlier than 6 years before, average intensity of diffuse pain ≥ 50 mm of Visual Analgue Scale (VAS), on a stable low dose of amitriptyline (10 mg/day) in the preceding 3 months and paracetamol 1g on demand for the FMS pain peaks [36,43]; exclusion of any concurrent major psychiatric disorder; exclusion of any medical conditions able to interfere with the sensory evaluation (hypertension, diabetes) [40,48]; e) informed, written consent to participate in the study.

Further inclusion criteria for the specific groups were as follows:

2.2.1. G*roup (1)(FMS)*: exclusion of any other concurrent pain condition except FMS;

2.2.2. G*roup (2)(FMS+IBS)*: IBS diagnosed by a gastroenterologist at least 1 year previously (Rome II criteria for diagnosis performed before 2006, Rome III for all subsequent diagnoses) [17,21], symptoms starting maximum 5 years before, not currently under treatment; exclusion of any other concurrent pain condition except FMS and IBS;

2.2.3. Group (3)(FMS+Dys): a diagnosis of primary dysmenorrhea performed by a gynecologist not earlier than 5 years before, not currently under hormonal treatment [27]; exclusion of any other concurrent pain condition except FMS and dysmenorrhea;

2.2.4. G*roup (4)(FMS+Endo):* the same as for group (3) except that dysmenorrhea had to be secondary to endometriosis, laparoscopically documented [27];

2.2.5. G*roup (5)(FMS+Div)*: a diagnosis of sigmoid colon diverticulosis [documented through abdominal Computerized Tomography (CT) scan] not earlier than 5 years previously, with at least 1 episode of acute/subacute diverticulitis in the past 6 months, treated medically [38]; exclusion of any other concurrent pain condition except FMS and diverticulosis/diverticulitis.

Verification of inclusion criteria was performed by the investigators at the first visit based on medical history, physical examination and review of previous medical records (Suppl. Table 1). A total of 142 patients meeting these criteria entered in the study:

FMS-only [n. 33, mean age: 36.7 ± 4.5SD years]

FMS+IBS [n. 29, mean age: 35.5 ± 4.8 (SD) yrs]

FMS+Dys [n. 31, mean age: 34.8 ± 5.1 yrs]

FMS+Endo [n. 25, mean age: 35.2 ± 3.9 yrs]

FMS+Div [n. 24, mean age: 37.8 ± 2.5 yrs]

Patients of all groups did not differ regarding mean age.

The study was divided in two phases, for a global duration of 16-24 months for each patient.

2.3. Phase 1. Pain symptoms and sensory evaluation in all groups

Patients of all groups underwent a prospective 6-month evaluation of their FMS pain symptoms:

i) number of FMS pain peaks (“flares”, to calculate their mean monthly number),

ii) average intensity of the diffuse musculoskeletal pain from FMS on a Visual Analogue Scale (VAS)(self-described average) [13];

iii) drug consumption for the diffuse musculoskeletal pain peaks (to calculate their mean monthly number).

Patients with internal organ comorbidities underwent evaluation also of their pain visceral symptoms:

i) IBS pain days and their intensity (in the FMS+IBS group). Patients completed a structured questionnaire answering a number of questions in the case of IBS pain [day of occurrence – to calculate the number of ‘‘Pain Days from IBS” – and pain characteristics, including intensity (VAS)][27];

ii) number of painful menstrual cycles (in both the FMS+Dys group and FMS+Endo group). Patients completed a structured questionnaire to keep track of their menstrual cycle month by month [date of start and approximate end of menstruation, current pain intensity (to calculate the number of painful menstrual cycles, i.e., cycles whose intensity exceeded 60 mm of VAS)][27];

iii) number and intensity of abdominal pain episodes from colon diverticulitis. Patients completed a structured questionnaire to make note of any episode of acute abdominal pain (day of occurrence, its intensity by VAS scale).

At the end of this 6-month prospective evaluation period, patients of all groups underwent evaluation of pain sensitivity:

- at the 18 TePs through measurement of pressure pain thresholds (PPTs) via Fischer’s algometer (to calculate the mean PPT in all points) [20];

- in areas outside the TePs (control areas), i.e., in 3 body sites: trapezius, deltoid and quadriceps of one side, through measurement of electrical (EPTs) and pressure pain thresholds in muscle and of electrical pain thresholds in overlying subcutis and skin [3].

2.4. Phase 2. Effects of treatment vs no treatment of the visceral pain condition on FMS symptoms and pain sensitivity in comorbid patients

This second part of the study was designed to assess the impact of visceral pain treatment on the FMS condition.

2.4.1. Dietary treatment of IBS in FMS+IBS patients. According to a protocol already established in a previous study in patients with comorbid visceral pain conditions [49], two-three months after the end of the 6-month prospective study, n. 19 patients started a 6-month dietary regimen for their IBS, as prescribed by their gastroenterologist, while the remaining 10 patients chose to not follow any specific diet [31]. Three months after discontinuation of the diet, and at a comparable time point in patients not undergoing any diet, all were requested to record their IBS pain and FMS pain for a further 6-month period (6-POST), at the end of which all thresholds were re-measured. IBS and FMS pain symptoms relative to this period were compared with those relative to the 6-month period (6-PRE) preceding the start of IBS dietary treatment. Thresholds at the end of 6-POST and 6-PRE were compared.

2.4.2. Hormonal treatment of primary dysmenorrhea in FMS+Dys patients. One-three months after the end of the 6-month prospective study, n. 20 patients started a

6-month hormonal treatment for their dysmenorrhea upon prescription by a gynaecologist while the remaining 11 patients were not willing to undergo such a therapy [27]. Three months after discontinuation of the treatment (to avoid any possible residual interference of the exogenous hormones on pain sensitivity) [4], or at a comparable time point in patients not undergoing therapy, patients were requested to record their Dys pain and FMS pain for a further 6-month period (6-POST), at the end of which all thresholds were re-measured. Dys and FMS pain symptoms relative to this period were compared with those relative to the 6-month period (6-PRE) preceding the start of Dys hormonal treatment. Thresholds at the end of 6-POST and 6-PRE were compared.

2.4.3. Laser treatment of endometriotic lesions in secondary dysmenorrhea in FMS+Endo patients. One–two months after the end of the 6-month prospective study, n. 12 patients with FMS+Endo were subjected to laser treatment of their endometriotic lesions in the course of laparoscopy, as prescribed by their gynaecologist, while the remaining 13 chose to not undergo such a therapy [16]. Three months after laser intervention, and at a comparable time point in patients not undergoing treatment, all patients were requested to monitor their menstrual pain and FMS pain for further 6-months, after which all thresholds were remeasured. Pain symptoms, for both dysmenorrhea and FMS, and pain thresholds pre and post treatment were compared.

2.4.4. Surgical treatment of diverticulosis in abdominal pain from diverticulitis in FMS+Div patients. One–two months after the end of the 6-month prospective study,

n. 9 patients with FMS+Div underwent surgery for their diverticulosis, while the remaining 15 patients chose to not undergo surgery [38]. Three months after surgery or at a comparable time point in patients not undergoing this interventional therapy, all were requested to monitor their abdominal pain and FMS pain for further 6-months, after which all thresholds were remeasured. Pain symptoms, for both abdominal pain and FMS pain, and pain thresholds pre and post treatment were compared. Surgery consisted of anterior sigma resection in a one-stage procedure, through a vertical xifo-pubic incision.

Patients of all groups were regularly monitored throughout the study period. They came to control visits at the center every 6 months, and were regularly contacted by phone by the health care personnel of the center every month, to verify the correct procedure of the protocol, offer additional material for the collection of data if needed (e.g., diary sheets), note any adverse event or new circumstance (e.g., new health problem, hospitalization) [27] and verify that no change in the therapy regimen had occurred which could intefere with the variables under evaluation.

2.5. Pain threshold measurement to electrical stimulation

A computerized constant current electrical stimulator (R.S.D. Stimulator, prototype, Florence 1997) was used, to deliver 18-ms trains of 0.5-ms monophasic square wave pulses, frequency 310 Hz, automatically every 2 s, to the somatic tissues of the body wall, through different electrodes for the superficial vs deep layers. Surface electrodes were employed for the skin, consisting of a 10-mm diameter circular plate

in Ag/AgCl (reference electrode) and a cylinder in Ag/AgCl with a 0.3 mm-diameter base (stimulating electrode), placed 1 cm apart on the skin surface with interposition of conductor paste. Needle electrodes were used for the subcutis and skin, i.e., two monopolar needles, 0.3 mm in diameter, isolated with Teflon their whole length except for 2 mm at the tip. They were inserted vertically, 1.5 cm apart, just below the skin surface for subcutis measurement and deep under the fascia for muscle measurement, their intramuscular position verified by observing electrode movement under voluntary contraction and/or low intensity electrical stimulation.

The evaluated sites were the: lateral aspect of the upper border of the trapezius (not coinciding with the TeP site, with electrodes placed in the horizontal direction), lower half of the deltoid and lowest third of the quadriceps (anterior aspect of the thigh). The method of the limits was applied for measurement of thresholds in each tissue at every site, to record typical pain sensations in each tissue, i.e., pricking pain for skin, linearly radiating prickling pain for subcutis and cramplike pain for muscle, according to a procedure already described in detail in previous publications [3,8,24,26,27,28].

During all measurements, patients lay comfortably on an adjustable examination bed in a quiet room. Measurements were always performed in the pain-free interval, with a wash-out of at least 48 hours from any symptomatic pain treatment, at the same time of day (10:00– 12:00 a.m.) by an experimenter blind to the group the patient belonged to.

2.6. Pain threshold measurement to pressure stimulation

A pressure dynamometer was used for the evaluation (Fischer's algometer, Pain Diagnostic and Treatment, Inc., Great Neck, NY) [20]. The 1-cm diameter rounded probe of the instrument was placed perpendicularly on each evaluation site, the pressure was increased by 0.1 kg-f/s until the patient reported a painful sensation for the first time, the corresponding kg-f value was considered as the pressure pain threshold for that site. Evaluation sites were the 18 TePs and the trapezius, deltoid and quadriceps muscles of one side (control sites). Two different points were evaluated in each of these three muscles, i.e., lateral and medial for trapezius, and upper and lower for deltoid and quadriceps [3,25].

2.7. Statistical analysis

For parameters: age, number of FMS flares, FMS pain intensity, analgesic consumption for FMS pain, number of IBS pain days, intensity of IBS pain, number of painful menstrual cycles, number and intensity of abdominal pain episodes from diverticulitis, means ± standard deviation (SD) were calculated for all patient groups. In each patient, the mean was calculated of: all PPTs at the 18 TePs; all values recorded at trapezius, deltoid and quadriceps for electrical and pressure pain thresholds (separately for skin, subcutis and muscle).

Means ± SD of all thresholds were then calculated for all patient groups. The Shapiro-Wilk test was applied to test normal distribution of variables. Normal distribution was ascertained for all variables except: drug consumption for FMS

flares, electrical skin thresholds and number of painful menstrual cycles. The comparison among groups for each parameter, at each detection time, was performed via 1-way ANOVA for normally distributed variables and Kruskal-Wallis Test for non-normally distributed variables. In each group, the comparison of the same parameter before and after therapy was performed via Student's t-test for paired samples for normally distributed variables and Wilcoxon matched-pairs signed-ranks test for non-normally distributed variables. In basal conditions, in each comorbid group, the possible correlation between parameters of visceral pain (number of IBS pain days, intensity of IBS pain, number of painful menstrual cycles and of painful abdominal episodes from diverticulitis) and FMS parameters and pain sensitivity (number of FMS flares, intensity of diffuse musculoskeletal pain, drug consumption for FMS flares, pain thresholds at all sites) was explored through the linear correlation test. The level of significance was established at $P<0.05$.

3. Results

3.1. FMS parameters and pain sensitivity in basal conditions in all groups (Figure 1)

3.1.1. FMS flares. There was a significant trend for variation of the mean monthly number of FMS flares among groups in basal conditions ($P<0.0001$). Flares were significantly more numerous in all comorbid groups vs the FMS only group ($P<0.001$).

3.1.2. Intensity of FMS pain. There was a significant trend for variation of the average intensity of FMS pain among groups in basal conditions (P<0.02). All comorbid groups had higher intensities than the FMS group, the difference was significant for the FMS+Div group (P<0.01).

3.1.3. Drug consumption for FMS pain. There was a significant trend for variation of the mean monthly drug consumption for FMS pain among groups in basal conditions (P<0.0001). Consumption was significantly higher in all comorbid groups vs the FMS group (P<0.001).

3.1.4. Pressure Pain Thresholds in TePs. The trend for variation of the mean pressure pain thresholds at the 18 fibromyalgic tender points was significant among groups (P<0.007). Thresholds were significantly lower in all comorbid groups vs the FMS only group (P<0.05).

3.1.5. Electrical skin pain thresholds. Thresholds in comorbid groups were slightly lower than in the FMS only group, but the difference was not significant.

3.1.6. Electrical subcutis pain thresholds. There was a significant trend for variation of the electrical pain thresholds in the subcutis (P<0.007). Thresholds were significantly lower in all comorbid groups compared to the FMS only group (P<0.05).

3.1.7. Electrical muscle pain thresholds. There was a significant trend for variation of the electrical pain thresholds in the muscle (P<0.007). Thresholds were significantly lower in all comorbid groups compared to the FMS only group (P<0.05).

3.1.8. Pressure muscle pain thresholds. There was a significant trend for variation of the pressure pain thresholds in the muscle (P<0.005). Thresholds were significantly lower in all comorbid groups compared to the FMS only group (P<0.05).

3.2. Visceral pain vs Fibromyalgia pain and pain sensitivity in basal conditions

3.2.1. FMS+IBS. In fibromyalgia patients comorbid with IBS, a significant direct linear correlation was found between the number of IBS days and: mean monthly number of FMS flares [Y = 0.17 X+2.537; (r) = 0.9306; P<0.0001], average intensity of FMS pain [Y = 0.3134X+62.136; (r) = 0.6180; P<0.0005] and mean monthly number of drug consumption for FMS pain [Y = 0.06662X+ 4.798; (r) = 0.8485; P<0.0001] relative to the evaluation period of 6 months preceding the start of therapy (6-PRE).

A significant inverse linear correlation was found between the number of IBS days of the 6-PRE evaluation period and: PPTs in TePs [Y = -0.02050X+2.458; (r) = -0.7959; P<0.0001], electrical muscle pain thresholds [Y = -0.02487X+2.921; (r) = -0.8839; P<0.0001] and muscle pressure pain thresholds [Y = -0.02597X+3.092; (r) = -0.8294; P<0.0001] recorded at the end of 6-PRE.

3.2.2. FMS+Dys. In fibromyalgia patients comorbid with primary dysmenorrhea (Dys), a significant direct linear correlation was found between the number of painful menstrual cycles and: mean monthly number of FMS flares [Y = 3.251X-3.166; (r) = 0.7654; P<0.0001], intensity of FMS pain [Y= 10.678X + 27.452; (r) = 0.8484;

P<0.0001] and mean monthly number of drug consumption for FMS pain [Y =2.587X -3.942; (r) = 0.8939; P<0.0001] relative to the 6-PRE evaluation period.

A significant inverse linear correlation was found between the number of painful menstrual cycles of the 6-PRE evaluation period and: PPTs in TePs [Y= -0.3236X+2.951; (r) = -0.7079; P<0.0001], electrical muscle pain thresholds [Y= -0.3379X+3.205; (r) = -0.8392; P< 0.0001] and pressure muscle pain thresholds [Y = -0.3334X+3.344; (r) = -0.8712; P<0.0001] recorded at the end of 6-PRE.

3.2.3. FMS+Endo. In fibromyalgia patients comorbid with dysmenorrhea secondary to endometriosis a significant direct linear correlation was found between the number of painful menstrual cycles and: mean monthly number of FMS flares [Y = 3.670X-5.231; (r) = 0.7335; P<0.0001], average intensity of FMS pain [Y=8.552X+39.212; (r) = 0.6564; P<0.0005] and mean monthly number of drug consumption for FMS pain [Y = 1.698X+1.038; (r) = 0.5712; P<0.003] relative to the 6-PRE evaluation period.

A significant inverse linear correlation was found between the number of painful menstrual cycles of the 6-PRE evaluation period and: PPTs in TePs [Y = -0.3544X+3.027; (r) = -0.8081; P<0.0001], electrical muscle pain thresholds [Y = -0.3527X+3.223; (r) = -0.7875; P<0.0001] and muscle pressure pain thresholds [Y = -0.267X+2.923; (r) = -0.4689; P<0.02] recorded at the end of 6-PRE.

3.2.4. FMS+DIV. In fibromyalgia patients comorbid with colon diverticulosis, a significant direct linear correlation was found between the number of episodes of acute abdominal pain from diverticulitis and: mean monthly number of FMS flares [Y = 4.358X+4.960; (r) = 0.9181; P<0.0001] and mean monthly number of drug

consumption for FMS pain [Y = 1.211X + 6.865; (r) = 0.4441; P<0.03] in the 6-PRE evaluation period.

A significant inverse linear correlation was found between the number of episodes of acute abdominal pain from diverticulitis in the 6-PRE evaluation period and: PPTs in TePs [Y = -0.3349X+1.882; (r) = -0.7701; P<0.0001], electrical muscle pain thresholds [Y = -0.3202X+2.024; (r) = -0.6556; P<0.0006] and pressure muscle pain thresholds [Y = -0.3477X+2.228; (r) = -0.6605; P<0.0005).

3.3. FMS parameters and pain sensitivity in comorbid patients before and after visceral pain therapy or no therapy

3.3.1. FMS+IBS (Figure 2). In the 6-PRE evaluation period, in FMS+IBS patients subsequently undergoing dietary treatment for IBS for 6 months, the number of IBS days was 55.21 ± 11.27 and the intensity of IBS abdominal pain was 44.84 ± 11.74 (mm of VAS). In the six months after the end of IBS treatment, there was a significant reduction of both number of IBS pain days (26.37 ± 8.12, P<0.0001) and IBS pain intensity (25.89 ± 7.18 mm, P<0.0001). In contrast, in FMS+IBS patients not undergoing IBS dietary treatment, no significant change was observed in both the number of IBS days and intensity of IBS pain between the 6-PRE and 6-POST evaluation periods (number of IBS days: 54 ± 15.32 before, 54.9 ± 13.20 after; intensity of IBS pain: 41.5 ± 3.84 mm before, 40.1 ± 4.1 mm after).

In FMS+IBS patients undergoing IBS dietary treatment, but not in FMS+IBS patients not treated for their IBS, a significant reduction was observed, after treatment, of the

mean monthly number number of FMS flares, intensity of FMS pain and mean monthly drug consumption to treat it (P<0.0001) and a significant increase of PPTs in TePs (P<0.0001), electrical pain thresholds in skin (P<0.0003), subcutis and muscle (P<0.0005) and pressure pain thresholds in muscle (P<0.0001).

3.3.2. FMS+Dys (Figure 3). In the 6-PRE evaluation period, FMS+Dys patients who subsequently underwent a hormonal treatment for dysmenorrhea (for 6 months) had reported 4.9 ± 0.72 painful menstrual cycles. In the six months subsequent to suspension of the 6-month hormonal treatment of dysmenorrhea they reported 0.9 ± 0.72 painful menstrual cycles (significant reduction, P<0.0001). In contrast, in FMS patients + dysmenorrhea not undergoing any hormonal treatment, the number of painful menstrual cycles in the 6-PRE period did not differ significantly from that of the 6-POST period (4.91 ± 0.83 vs 5.1 ± 0.70).

In FMS+Dys patients undergoing hormonal treatment for dysmenorrhea, but not in FMS+Dys patients not treated for their dysmenorrhea, a significant reduction was observed, after treatment, of the mean monthly number of FMS flares, intensity of FMS pain and mean monthly drug consumption to treat FMS pain (P<0.0001) and a significant increase of PPTs in TePs (P<0.0001), electrical pain thresholds in skin (P<0.002), subcutis (P<0.0006) and muscle (P<0.0003) and pressure pain thresholds in muscle (P<0.0004).

3.3.3. FMS+Endo (Figure 4). In the 6-PRE evaluation period, FMS+Endo patients who subsequently underwent laser ablation of endometriotic lesions had reported 4.83 ± 0.72 painful menstrual cycles. In the 6-month evaluation period subsequent to

surgery, they reported 1.33 ± 0.65 painful menstrual cycles (significant reduction, P<0.0006). In contrast, in FMS+Endo patients not undergoing laser treatment for endometriosis, the number of painful menstrual cycles in the 6-PRE and 6-POST evaluation periods did not differ significantly (4.69 ± 0.85 vs 4.85 ± 0.90).

In FMS+Endo patients undergoing laser treatment of lesions, but not in FMS+Endo not treated for their endo, a significant reduction was observed, after treatment, of the mean monthly number of FMS flares (P<0.003), intensity of FMS pain (P<0.0001) and drug consumption to treat FMS pain (P<0.0006) and a significant increase of PPTs in TePs (P<0.02), electrical pain thresholds in skin (P<0.004), subcutis (P<0.001) and muscle (P<0.0005) and pressure pain thresholds in muscle (P<0.002).

3.3.4. FMS+Div (Figure 5). In the 6-PRE evaluation period, FMS patients with colon diverticulosis had had 1.78 ± 0.83 episodes of acute abdominal pain from diverticulitis, the average intensity of the pain was 80.83 ± 6.48mm of VAS. In the 6-month evaluation period subsequent to surgery, they reported no episodes of abdominal pain (P<0.0003). In the FMS group with diverticulosis who did not undergo surgery, no significant difference was recorded between the 6-PRE and 6-POST evaluation periods regarding the number of episodes of acute abdominal pain from diverticulitis (1.53 ± 0.74 vs 1.33 ± 0.49 episodes) and their average intensity (79.5 ± 6.52 vs 78.6 ± 5.08). In FMS+Div patients undergoing surgery for diverticulosis, but not in FMS+Div patients not subjected to surgery, a significant reduction was observed, after treatment, of the mean monthly number of FMS flares (P<0.03), intensity of FMS pain (P<0.0007) and mean monthly drug consumption to

treat FMS pain (P<0.004) and a significant increase of PPTs in TePs (P<0.04), electrical pain thresholds in skin (P<0.02), subcutis (P<0.02) and muscle (P<0.0007) and pressure pain thresholds in muscle (P<0.05).

4. Discussion

In this study in fibromyalgia patients, the presence of a concurrent visceral pain disorder is associated with a significantly higher level of FMS spontaneous pain and symptomatic drug consumption to treat it, as well as a significantly increased level of hypersensitivity to pain in deep somatic tissues in both typically painful FMS areas (TePs) and nonpainful control areas with respect to fibromyalgia without associated visceral pain. Specific treatment of the visceral pain disorder, resulting in improvement of the visceral pain symptoms, also produces a significant decrease in the spontaneous FMS pain and a tissue desensitization, as testified by increased pain thresholds in all tissues at all levels. In each comorbid group, the amount of perceived visceral pain (frequency of episodes) is directly correlated with the extent of both the spontaneous FMS pain and the level of hypersensitivity at muscle level in painful and nonpainful areas. These results suggest that the examined visceral pain disorders (IBS, primary and secondary dysmenorrhea, diverticulitis) act as triggering factors for FMS pain symptoms. They confirm previous results in FMS patients who were comorbid with another visceral pain condition, i.e., symptomatic gallbladder calculosis; in these patients, the number of biliary colics correlated with FMS pain and muscle hypersensitivity [13]. Surgical removal of the gallbladder, after a transitory

worsening of muscle symptoms in the first 3 postoperative months, probably due to the nociceptive input from the surgical procedure, produced a significant long-term (from the 3rd to the 12th month) improvement of the FMS global symptomatology, in terms of both spontaneous FMS pain and muscle hypersensitivity in painful and nonpainful areas. The results of the present study are also in line with those relative to FMS comorbidity with somatic peripheral pain conditions, such as myofascial pain syndromes from trigger points and painful joints [3,23]. Previous studies in these comorbid patients, in fact, showed that local treatment of the trigger points and of the painful joints not only improved the somatic pain conditions but also induced a significant reduction of FMS pain symptoms and diffuse muscle hypersensitivity. In the present study, as well as in the mentioned previous studies, the impact of comorbidities was evaluated only on musculoskeletal pain and hyperalgesia parameters of FMS, not addressing other specific nonpain FMS symptoms such as sleep disturbance, fatigue or mood disorders [50]. A possible effect of visceral pain comorbidities and their treatment on these other important symptoms of the syndrome thus remains to be assessed in further systematic research in the field. The enhanced FMS pain and hyperalgesia here found in FMS patients comorbid with visceral pain disorders is probably the result of the central effect of the nociceptive input from the visceral pain periphery on sensory neurons, with enhancement of the level of central sensitization typical of FMS [22]. Peripheral sensitization at visceral level in repeated visceral episodes as described here is also likely to contribute to the phenomenon, by modulating the extent of the consequent central sensitization [10]. Three of the

visceral pain conditions considered in the present study: IBS, primary dysmenorrhea and dysmenorrhea secondary to endometriosis have been shown to involve, per se (thus even in the absence of fibromyalgia), a certain degree of generalized hypersensitivity to pain at deep somatic - muscle - level [6,8,9,26]. The improvement of the diffuse hyperalgesia after their specific treatment could thus also be a direct effect of the cure of the visceral pain condition; further studies evaluating the impact of visceral pain treatment in patients with IBS, dysmenorrhea and endometrosis without FMS should be undertaken to precisely assess this effect. It must be underlined, however, that in our FMS+visceral pain comorbid patients, the effects of the visceral pain treatment have also been in terms of improvement of the typical spontaneous FMS pain, an effect which can only be indirect, probably mediated, as already stated, through a reduction of the algogenic input from the viscera towards the central nervous system. Regarding diverticulitis, though no studies appear to have been previously conducted to assess sensitivity in nonpainful areas in patients not suffering from fibromyalgia, there are no clinical indications of diffuse pain hypersensitivity, but only of regional hyperalgesia in the referred abdominal areas, as is the general rule in visceral nociception [5,14,29,49]. Thus, here again, the positive impact of diverticulitis treatment onto FMS symptoms seems to be an indirect effect mediated via the central nervous system. Along with increased pain processing in the CNS, there is evidence of impaired endogenous pain inhibition in FMS, i.e., dysfunction of the neural systems that contribute to the descending inhibitory patways [32]. In this context, it cannot be excluded that the positive effect of the

suppression/reduction of the peripheral visceral nociceptive input on FMS pain symptoms is also contributed to by an improvement of central pain modulation mechanisms.

There is increasing evidence that some common and highly prevalent pain conditions coexist [37,41]. Over the past twenty years epidemiological studies have documented the presence of more than one chronic pain condition in subjects with pain. These results suggest that chronic pains may not be localized disorders, but may share symptoms and mechanisms that involve a general central nervous system dysfunction as well as disorder-specific symptoms. The U.S. Congress and National Institutes of Health recently coined the term Chronic Overlapping Pain Conditions (COPCs) to describe the clinical state of significant overlap among chronic pain disorders [46], a term fully applying to the comorbid patients examined in the present study. In the clinical setting each chronic pain condition is typically treated as a single entity. However, the overlap of chronic pain conditions raises the question whether these conditions share common pathways of vulnerability, and efforts are currently under way to develop a multi-dimensional pain taxonomy system that recognizes the multiple comorbid conditions which are characteristic of many patients suffering from chronic pain syndromes [19]. Recently, for instance, a frequent comorbidity has been described of joint hypermobility Ehlers-Danlos Syndrome (EDS) with the majority of pain conditions described in the present study, i.e., fibromyalgia or chronic widespread pain, IBS and dysmenorrhea; a common heritable disorder of connective tissue has been suggested and a possible common pathophysiological

substrate hypothesized for pain symptoms of all conditions, residing in central sensitization mechanisms [15,18,44]. Patients of this study were not assessed for EDS, but the possibility of this association is worth systematic consideration in future studies in fibromyalgia when evaluating the comorbidity range of the condition. At present there is very little attention given to the overlap of chronic pain conditions when patients are treated for pain in clinical practice or recruited for clinical trials. The current study focusing on the overlap of FMS and visceral pain suggests that careful assessment of all concurrent visceral comorbidities in FMS and their systematic treatment should be an integral part of the management strategy of the syndrome. The results of this study have important implications regarding the clinical management of patients with COPCs and the design of clinical pain trials, and emphasize the importance of recognizing COPCs rather than focusing on a single pain condition both in the context of diagnosis as well as treatment.

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Figure legends

Fig. 1. Pain symptoms from FMS [A. Mean monthly number of FMS peak episodes; B. Average intensity of FMS pain; C. Mean monthly number of analgesics taken for FMS pain] in a 6-month evaluation period, and somatic pain sensitivity measured at the end of this period [D. Mean Pressure Pain Thresholds (PPTs) at the 18 Tender Points (TePs); E. Pain thresholds to electrical stimulation in skin (mean of values recorded in the skin overlying trapezius, deltoid and quadriceps); F. Pain thresholds to electrical stimulation in subcutis (mean of values recorded in the subcutis overlying trapezius, deltoid and quadriceps); G. Pain thresholds to electrical stimulation in muscle (mean of values recorded in trapezius, deltoid and quadriceps); H. Pain thresholds to pressure stimulation in muscle (mean of all recordings performed in trapezius, deltoid and quadriceps)] in patients with FMS-only [n. 33], FMS+IBS [n. 29], FMS+Dys [n. 31], FMS+Endo [n. 25] and FMS+Div [n. 24][Means ± SD]. Asterisks over SD bars refer to comparison of comorbid groups with the FMS only group. * = $P<0.05$; ** = $P<0.01$; *** = $P<0.001$.

Fig. 2. Fibromyalgia+Irrtable Bowel Syndrome (FMS+IBS). Pain symptoms from FMS and somatic pain sensitivity before and after dietary treatment of IBS (n. 19 patients) or no treatment of IBS (n. 10 patients). A. Mean monthly number of FMS peak episodes, B. Average intensity of FMS pain, C. Mean monthly number of analgesics taken for FMS, D. Mean Pressure Pain Thresholds (PPTs) at the 18 Tender Points (TePs); E. Pain thresholds to electrical stimulation in skin (mean of values

recorded in the skin overlying trapezius, deltoid and quadriceps); F. Pain thresholds to electrical stimulation in subcutis (mean of values recorded in the subcutis overlying trapezius, deltoid and quadriceps); G. Pain thresholds to electrical stimulation in muscle (mean of values recorded in trapezius, deltoid and quadriceps); H. Pain thresholds to pressure stimulation in muscle (mean of all recordings performed in trapezius, deltoid and quadriceps)] [Means ± SD]. Asterisks over SD bars refer to comparison of values before and after therapy (or no therapy). *** = P<0.001.

Fig. 3. Fibromyalgia+Dysmenorrhea (FMS+Dys). Pain symptoms from FMS and somatic pain sensitivity before and after hormonal treatment of dysmenorrhea (n. 20 patients) or no treatment of dysmenorrhea (n. 11 patients). Legend as for Fig. 2. ** =P<0.01; *** = P<0.001.

Fig. 4. Fibromyalgia+Endometriosis (FMS+Endo). Pain symptoms from FMS and somatic pain sensitivity before and after laser treatment of endometriosis (n. 12 patients) or no treatment of endometriosis (n. 13 patients). Legend as for Fig. 2. * = P<0.05; ** = P<0.01; *** = P<0.001.

Fig. 5. Fibromyalgia+Diverticulosis (FMS+Div). Pain symptoms from FMS and somatic pain sensitivity before and after surgical treatment of diverticulosis (n.9 patients) or no treatment of diverticulosis (n. 15 patients). Legend as for Fig. 2.* = P<0.05; ** = P<0.01; *** = P<0.001.

Summary:
Comorbid visceral pain in fibromyalgia patients involves increased musculoskeletal pain and diffuse somatic hyperalgesia, probably from enhanced central sensitization by the visceral noxious inputs.

Figure 1

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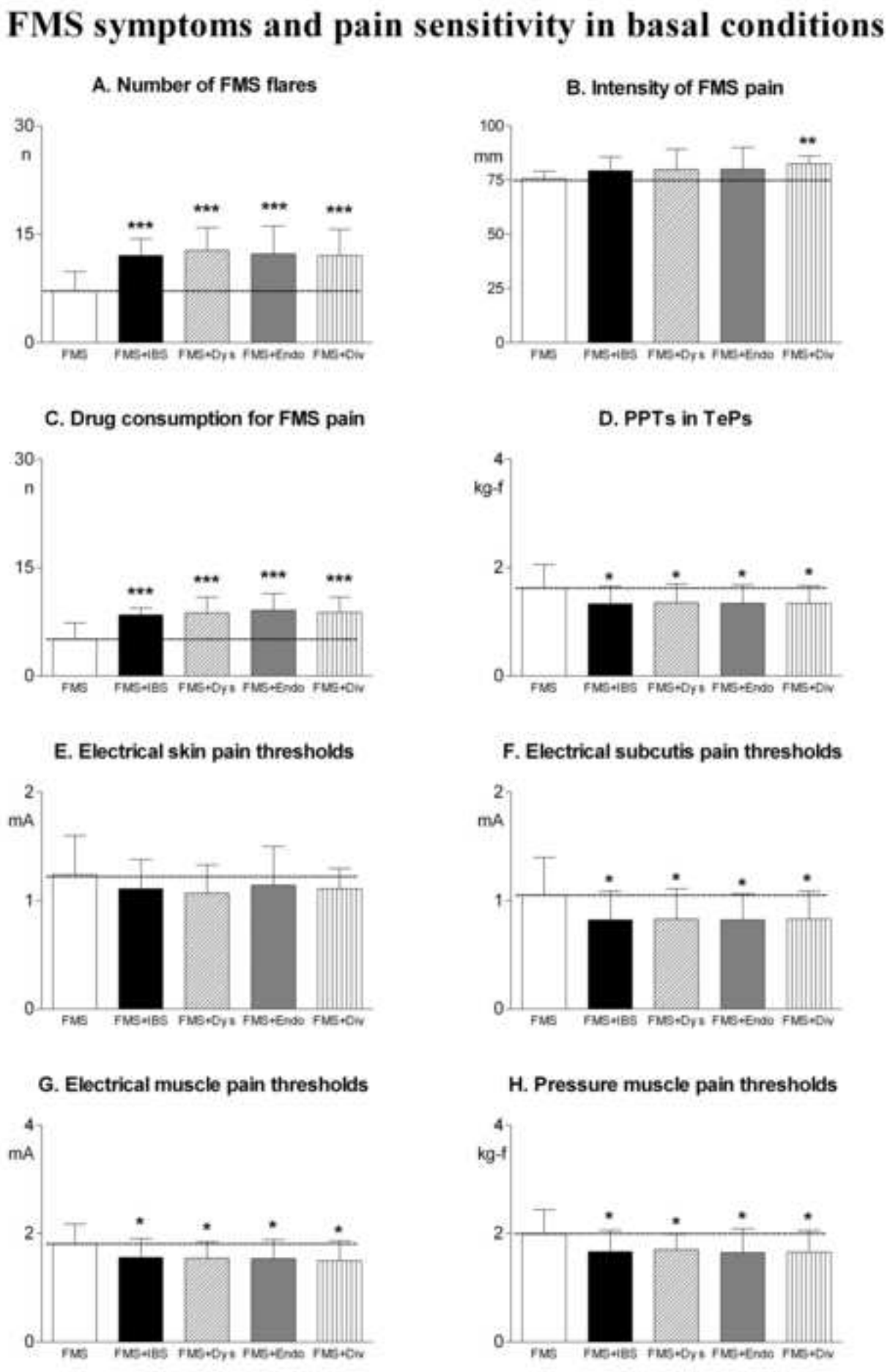

Figure 2

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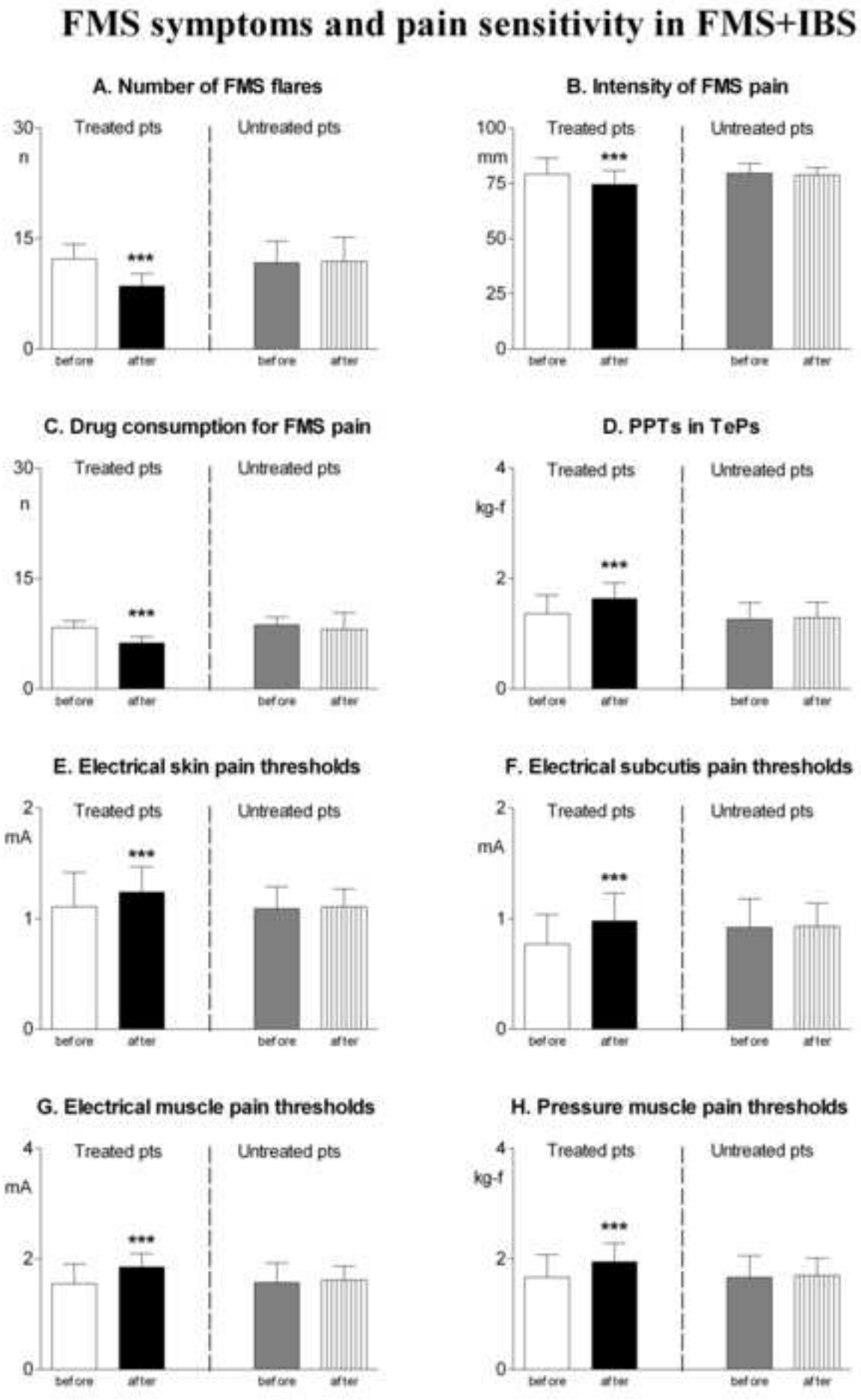

Figure 3

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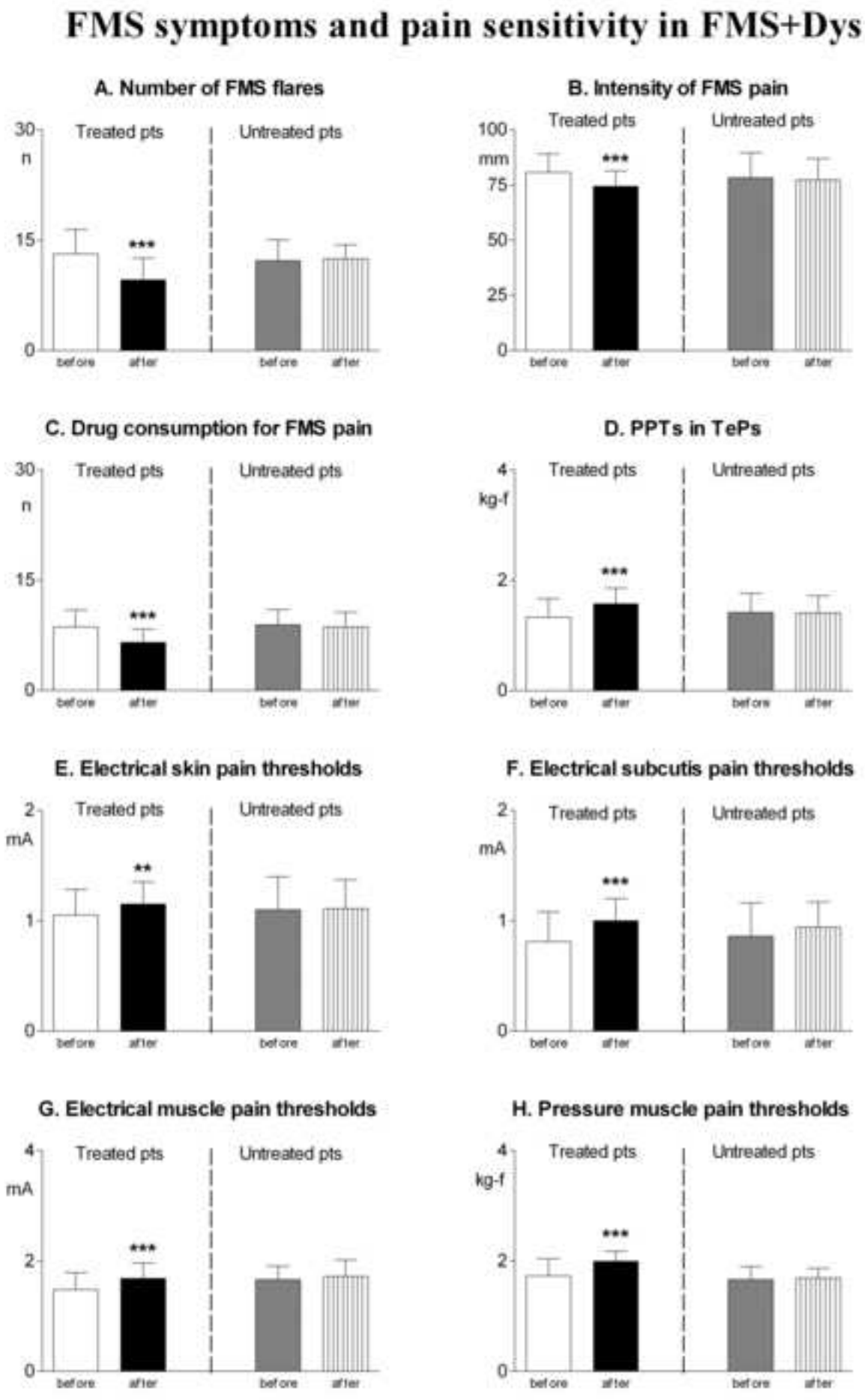

Figure 4

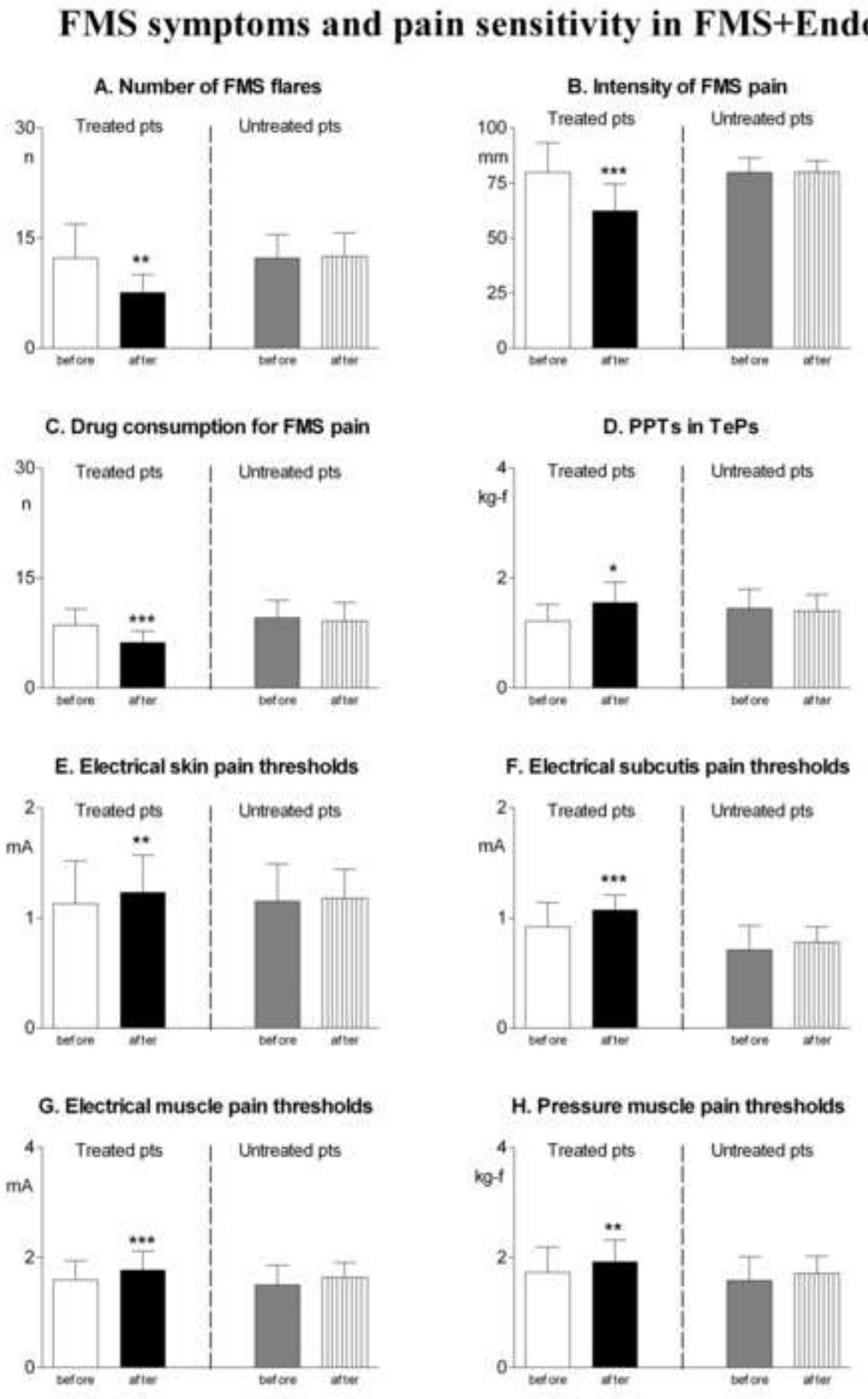

Figure 5

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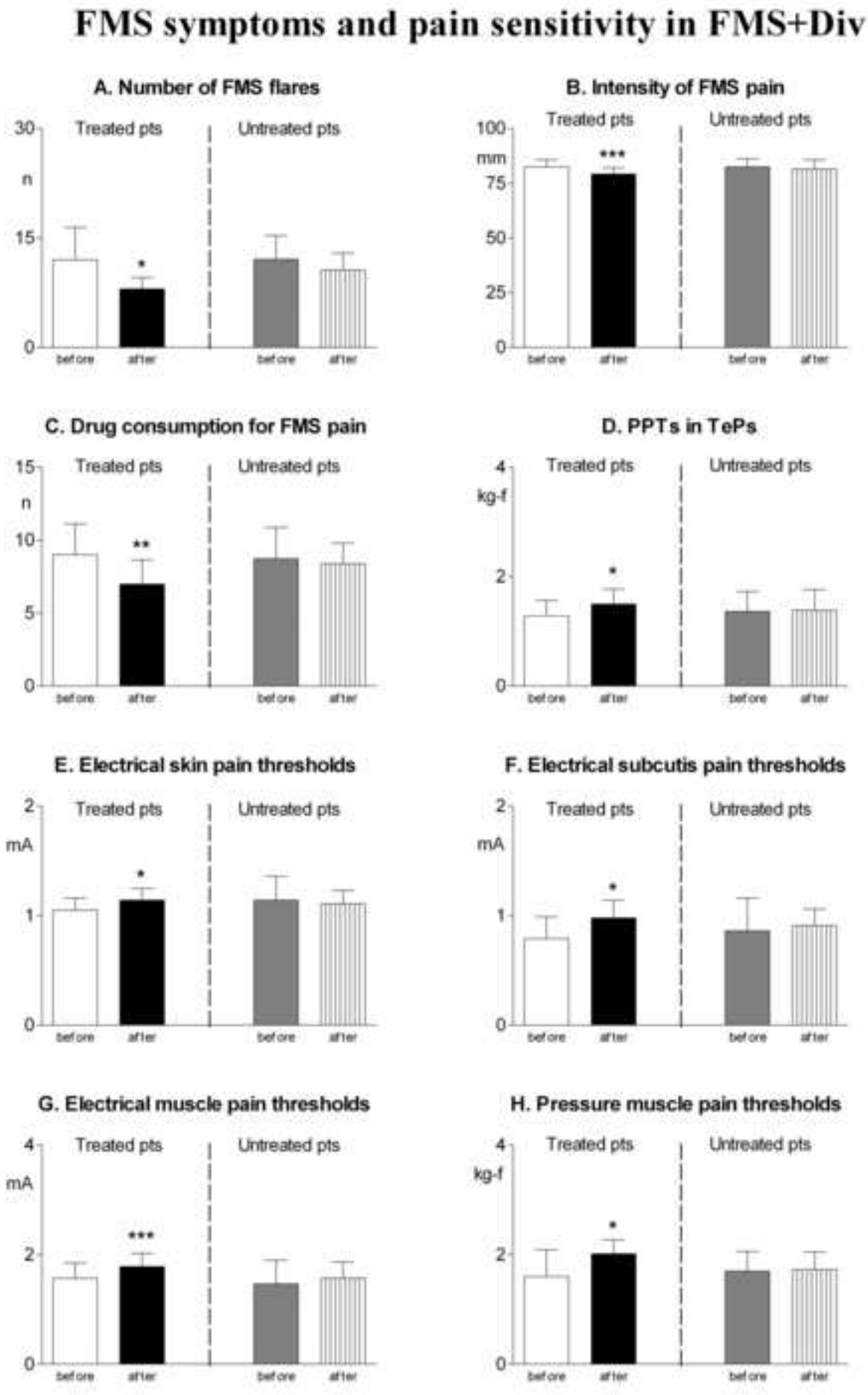

Table 1 - Recruitment and selection of patients

Number of patients	Criteria
825	Consecutive patients January 2006- December 2008, referred for a first visit to the Fibromyalgia Center (FC), by family physician or other specialist, for suspected or already diagnosed FMS
↓	
418	Patients with FMS diagnosis at first visit (remaining 407, diagnosis of: other rheumatic diseases, polyosteoarthritis, multiple myofascial pain syndromes, multiple column discopathies)
↓	
249	Patients with FMS already previously diagnosed by a specialist, confirmed by FC at first visit (remaining 169: new diagnosis of FMS by FC)
↓	
142	Patients with FMS meeting the inclusion criteria, recruited for the study*
33 (of 60)	FMS-only patients
29 (of 37)	FMS+IBS patients
31 (of 41)	FMS+Dys patients
25 (of 55)	FMS+Endo patients
24 (of 56)	FMS+Div patients

Drop-outs. FMS-only: in 2 patients, missing electrical subcutis and muscle thresholds for deltoid, in 1 patient, missing electrical subcutis and muscle thresholds for trapezius at last threshold evaluation (pain at insertion of electrodes)
FMS+IBS: in 3 patients, missing electrical subcutis and muscle thresholds for trapezius at first threshold evaluation (pain and/or bleeding at insertion of electrodes)
FMS+Dys: in 1 patient, missing electrical subcutis and muscle thresholds in quadriceps at last threshold evaluation (sense of fainting at insertion of electrodes)
FMS+Div: in 1 patient, missing electrical skin, subcitis and muscle thresholds for quadriceps at last threshold evaluation (skin irritation being treated locally with cortison), in 2 patients, missing electrical subcutis and muscle thresholds in deltoid and trapezius, respectively, at last threshold evaluation (bleeding at insertion of electrodes)

*First recruited patient: January 2006, last recruited patient: December 2008. Completion of study of last recruited patient: December 2010. December 2010-December 2014: all 142 subjects still patients at the center, undergoing regular control visits every 6 or 12 months for re-assessment of therapy. After December 2014: 85 patients no longer followed by the center, 57 still under periodic control till December 2016.

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