American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 18, No 7 (July), 2017: pp 835-843
Available online at www.jpain.org and www.sciencedirect.com

Lower Placebo Responses After Long-Term Exposure to Fibromyalgia Pain

Eva Kosek,[*,†] Annelie Rosen,[*] Serena Carville,[‡] Ernest Choy,[§] Richard H. Gracely,[¶] Hanke Marcus,[‖] Frank Petzke,[**] Martin Ingvar,[*] and Karin B. Jensen[*]

**Karolinska Institutet, Stockholm, Sweden.*
[†]Stockholm Spine Center, Stockholm, Sweden.
[‡]King's College, London, United Kingdom.
[§]Cardiff University School of Medicine, Cardiff, United Kingdom.
[¶]University of North Carolina, Chapel Hill, North Carolina.
[‖]University Hospital, Cologne, Germany.
***University of Göttingen, Göttingen, Germany.*

Abstract: **Knowledge about placebo mechanisms in patients with chronic pain is scarce. Fibromyalgia syndrome (FM) is associated with dysfunctions of central pain inhibition, and because placebo analgesia entails activation of endogenous pain inhibition, we hypothesized that long-term exposure to FM pain would negatively affect placebo responses. In our study we examined the placebo group (n = 37, mean age 45 years) from a 12-week, randomized, double-blind, placebo-controlled trial investigating the effects of milnacipran or placebo. Twenty-two patients were classified as placebo nonresponders and 15 as responders, according to the Patient Global Impression of Change scale. Primary outcome was the change in pressure pain sensitivity from baseline to post-treatment. Secondary outcomes included ratings of clinical pain (visual analog scale), FM effect (Fibromyalgia Impact Questionnaire), and pain drawing. Among placebo responders, longer FM duration was associated with smaller reductions in pressure pain sensitivity (r = .689, *P* = .004), but not among nonresponders (r = −.348, *P* = .112). In our study we showed that FM duration influences endogenous pain regulation, because pain levels and placebo-induced analgesia were negatively affected. Our results point to the importance of early FM interventions, because endogenous pain regulation may still be harnessed at that early time. Also, placebo-controlled trials should take FM duration into consideration when interpreting results.**

Perspective: ***This study presents a novel perspective on placebo analgesia, because placebo responses among patients with chronic pain were analyzed. Long-term exposure to fibromyalgia pain was associated with lower placebo analgesia, and the results show the importance of taking pain duration into account when interpreting the results from placebo-controlled trials.***

© 2017 The Authors. Published by Elsevier Inc. on behalf of the American Pain Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: *Placebo analgesia, fibromyalgia, long-term pain, chronic pain, pain inhibition.*

Received June 19, 2016; Revised February 13, 2017; Accepted February 21, 2017.
Clinical trial registration EudraCT 2004-004249-16.
This work was supported in part by the pharmaceutical company Pierre Fabre through financing of a placebo-controlled drug intervention study (EudraCT: 2004-004249-16).
The authors have no conflicts of interest to declare.
Address reprint requests to Karin B. Jensen, PhD, Nobels väg 9, D3, Karolinska Institutet, Stockholm 17176, Sweden. E-mail: Karin.Jensen@ki.se
1526-5900
© 2017 The Authors. Published by Elsevier Inc. on behalf of the American Pain Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
http://dx.doi.org/10.1016/j.jpain.2017.02.434

The ability to endure painful conditions depends largely on activation of endogenous pain inhibitory mechanisms in the central nervous system. Pain inhibition is therefore part of the normal pain response and modulates the relationship between incoming nociceptive signals and perceived pain. In common pain disorders, such as chronic low back pain and fibromyalgia syndrome (FM), there is evidence for augmented cerebral processing of pain.[2,15,20] In addition, FM pain has repeatedly been associated with impaired pain inhibition[25,30,32] and decreased activity within pain inhibitory pathways in the brain.[20,21] The

inability to activate endogenous pain inhibition is often referred to as 'disinhibition' and is a hallmark of FM pathophysiology.[20,30]

Placebo analgesia is a term that describes pain reduction in response to an inert treatment that mimics a genuine analgesic treatment (eg, sugar pill) by creating treatment expectations of relief. The neurobiological mechanisms of placebo analgesia were first described by Levine et al[34] and since then a large literature has verified the original findings by showing activation of cerebral pain inhibitory pathways during placebo analgesia[37,45] and endogenous release of opioids in the brain.[48]

Because placebo analgesia depends on activation of endogenous pain relief, and FM patients are characterized by dysfunctional pain inhibition, the presence of placebo responses among FM patients may seem paradoxical. In a recent meta-analysis, in which placebo responses in drug trials for FM and patients with peripheral diabetic neuropathy were compared, FM patients had relatively lower placebo responses than patients with neuropathy.[17] The authors speculate that the difference may reflect the underlying inability to recruit endogenous analgesia among FM patients, compared with patients with neuropathy who are not characterized by central disinhibition.[17] However, there was presence of some degree of placebo responses among FM patients,[17,18] and because there was considerable variance in responses between patients, it is possible that the ability to recruit endogenous pain inhibition varies as a function of pain chronification. Several studies have shown brain alterations in response to FM pain over time,[23,31] indicating a negative effect of long-term exposure to pain that is not attributable to normal aging. In our previous study, we found less gray matter volumes and less functional connectivity in the rostral anterior cingulate cortex (rACC) in patients with FM[23]; a key region for endogenous pain inhibition that is often activated during placebo analgesia.[5,10,37] Hence, it is possible that patients with FM display diminished placebo analgesia responses over time as a result of more severe effects on key regions for pain inhibition.

In this study, we investigated the placebo response in FM patients in relation to time since onset of widespread pain. In line with the evidence for dysfunctional endogenous pain regulation in FM, and more pronounced brain alterations over time, we hypothesized that patients with long exposure to FM symptoms would have lower placebo responses. To address this question, we used the placebo data from a double-blind, randomized, placebo-controlled clinical trial in which patients were treated with the selective noradrenalin serotonin reuptake inhibitor milnacipran, or placebo.

Methods

Patients

A total of 92 patients were randomized and included in the overall clinical trial; 46 were randomized to the placebo arm. Outcome data from 38 patients in the placebo group were available after treatment, yet 1 patient was excluded from the statistical analyses due to en passant neurological findings. Hence, all statistics are on the basis of 37 patients. Results from the overall clinical trial can be found in previous publications.[22,38] Patients eligible for inclusion were female, aged 18 to 55 years, fulfilling the American College of Rheumatology 1990 criteria for FM[47] and with a self-reported average weekly pain intensity of at least 40 mm on a 100-mm visual analog scale (VAS), ranging from "no pain" and "worst imaginable pain." Exclusion criteria included: presence of severe psychiatric illness, significant risk of suicide, a history of substance-, drug-, or alcohol abuse, significant cardiovascular/pulmonary disease (including electrocardiogram abnormalities and hypertension), liver disease, renal impairment, pregnancy, or breastfeeding. Therapies that could interfere with the tested treatment were prohibited (ie, antidepressants and mood stabilizers, analgesics; tramadol, codeine, dextropropoxyphene), strong opioids including patches, anesthetic transdermal patches, anticonvulsants, centrally acting relaxants, joint injections, trigger/tender point injections, biofeedback and transcutaneous electrical nerve stimulation. Paracetamol and dipyrone were allowed as rescue medicines and short-term use of zolpidem was allowed as treatment for insomnia. Nonsteroidal anti-inflammatory drugs were allowed under control from the study investigators. Rescue medications and nonsteroidal anti-inflammatory drugs had to be discontinued 48 hours before assessments of symptoms and pain sensitivity. This study was approved by the local ethics committee at each site, and informed consent was obtained before inclusion. Initial information about the study was given to patients via the phone, and then again during a meeting where the patient received written and oral information. Patients were informed that the study was aimed at assessing the effect of milnacipran on sensitivity to pressure and cerebral processing of pain. Milnacipran was described as an antidepressant with previously demonstrated positive effects on FM symptoms, exemplified by decreased pain, improved mood, quality of life, and physical function. Furthermore, patients were informed that the study was double blind and that each patient had a 50/50 likelihood of receiving milnacipran or placebo. Patients were informed that a common side-effect of milnacipran treatment is nausea, and could also read about rare side effects in the written information. Allocation of the medication was performed by study staff upon each study visit, by giving the patient a new box with pills.

Procedure

This study was a randomized, double-blind, placebo-controlled, parallel-group trial assessing the effects of 12 weeks of treatment with milnacipran or placebo (EudraCT number 2004-004249-16). Patients were mainly recruited from primary care at the different study sites; London (England), Cologne (Germany), and Stockholm (Sweden). A screening visit was scheduled 7 to 28 days

before study inclusion and consisted of a clinical examination, questionnaires, and laboratory tests to confirm eligibility. A second visit (baseline visit) was scheduled after at least 7 days, or the time needed for medication washout. During the second visit, baseline assessments were performed. The following day, patients returned for a brain scan and then started the treatment (milnacipran/placebo). After a 3-weeks dose escalation, patients had a 9-week fixed dose phase of milnacipran or placebo. Two follow-up visits were scheduled between baseline and study end, including checks of compliance, adverse events, pain ratings, and vital signs. Patients returned in week 12 (day 83 ± 1 day) for the evaluation of treatment effects followed by a 9-day down-titration phase.

Responder Classification

After treatment (week 12), patients rated their subjective impression of treatment effect, using the Patient Global Impression of Change (PGIC) questionnaire[19,39] with the options: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), and very much worse (7). Treatment responders were a priori defined as patients reporting any type of improvement (ie, PGIC 1, 2, or 3). Nonresponders were defined as patients having no change (ie, PGIC 4) or worsening of symptoms (ie, PGIC 5, 6, or 7). PGIC is a commonly used scale measuring the patients' subjective report of clinical improvement in relation to a given treatment.

Baseline Characteristics

To characterize patients at baseline, they rated the duration of their widespread pain (FM duration, months), as well as the degree of depressive symptoms (Beck Depression Inventory [BDI]),[3] anxiety (Spielberger State Trait Anxiety Inventory),[42] catastrophizing thoughts (subscale of the Coping Strategies Questionnaire [CSQ]),[8] and general health (complete 36-item short-form health survey, combination of mental and physical component).[46]

Primary Outcome: Pressure Pain Sensitivity (Amount of Pressure Required to Evoke Each Individual's Pain at VAS 50 mm)

The primary outcome of this trial was patients' change in pressure pain sensitivity from baseline to post-treatment (value calculated as: [post treatment pressure (kPa) − baseline pressure (kPa)]). Pressure stimulations were applied to the left thumbnail using an automated, pneumatic, computer-controlled stimulator with a plastic piston that applies pressure via a 1-cm^2 probe.[20] Patients were assessed for pressure pain sensitivity by receiving 1 ascending series of pressure stimuli and 1 randomized series. Pain intensity in response to each stimulus was rated on a 100-mm VAS, anchored with "no pain" and "worst imaginable pain." A polynomial regression function was used to determine each individual's representation of VAS 50 mm, on the basis of 15 randomized stimuli in the range between each patient's pain threshold and the first pressure that exceeded VAS 60 mm. The polynomial regression was used because the relationship between stimulus (pressure) and response (pain ratings) had nonlinear properties. The exact amount of pressure required to evoke each individual's pain at VAS 50 mm is referred to as P50.

Secondary Outcome Measures

Secondary outcome measures were collected before and after treatment and included: FM pain variability calculated as each patient's difference between weekly minimum and weekly maximum pain intensities (VAS 0–100 mm) at baseline; average weekly pain intensity (VAS); number of painful areas (pain drawing); effect of FM symptoms (Fibromyalgia Impact Questionnaire).[7]

Statistical Analyses

Differences at baseline, and differences from baseline to after treatment, were analyzed using 1-sample t-tests (within groups) and independent samples t-tests (between groups). Because of the nonparametric properties of VAS ratings, the pain ratings (average weekly pain, pain variability) and P50 were analyzed with Wilcoxon signed-rank tests (within groups) and Mann-Whitney U tests (between groups). Correlation analyses were performed using Spearman r coefficient (when ordinal measures were included), except for the correlation between FM duration and age, which was analyzed with Pearson r (continuous measures). All statistical analyses were performed using SPSS 23.0 (IBM Corp, Armonk, NY). The significance level was set as $P < .05$, 2-tailed.

Results

Patient Characteristics

Among all patients in the placebo arm of this clinical trial, 22 patients were nonresponders and 15 were responders according to the PGIC measure. The mean age across responders and nonresponders was 45 years, and patients had suffered from widespread pain for an average of 132 months (11 years; Table 1).

Baseline Comparisons Between Placebo Responders and Nonresponders

Placebo responders had lower ratings of depression (BDI) at baseline compared with nonresponders ($P = .015$), and less catastrophizing thoughts (CSQ) ($P = .021$). No significant differences were found in any other baseline variables between the groups (Table 1).

Change From Baseline to After Treatment for Placebo Responders and Nonresponders

Patients who reported a positive treatment response on the PGIC were significantly improved in almost all outcome measures from before treatment to after treatment, including FM effect (Fibromyalgia Impact

Table 1. Baseline Characteristics

Characteristic	Total (N = 37)	Nonresponders (N = 22)	Responders (N = 15)	Difference (P)
Age	45.14 ± 8.64	45.18 ± 8.75	45.07 ± 8.78	.969
FM duration	132.15 ± 94.15	142.86 ± 102.98	115 ± 79.75	.368
BDI	16.61 ± 9.82	19.80 ± 9.29	12.00 ± 8.91	.015*
CSQ	14.89 ± 8.02	17.36 ± 7.22	11.27 ± 7.97	.021*
SF-36	35.95 ± 16.74	33.18 ± 15.32	40 ± 18.42	.229
FIQ	64.40 ± 15.20	65.90 ± 11.91	62.21 ± 19.31	.447
STAI-T	47.05 ± 10.40	49.14 ± 10.38	44.00 ± 9.97	.142
Average weekly pain	67.84 ± 14.63	68.05 ± 15.00	67.53 ± 14.58	.865
Pain variability	44.76 ± 20.61	41.4 ± 21.40	49.67 ± 19.05	.143
Pain drawing	8.46 ± 2.12	8.55 ± 2.08	8.33 ± 2.32	.769
P50	395.63 ± 146.08	418.70 ± 147.15	361.80 ± 142.58	.272

Abbreviations: SF-36, 36-item short-form health survey; FIQ, Fibromyalgia Impact Questionnaire; STAI-T, State Trait Anxiety Inventory.
NOTE. Data are presented as mean ± SD except where otherwise noted. Age (years), FM duration (months), ratings of depression (BDI), catastrophizing (CSQ), general health (SF-36), effect of fibromyalgia (FIQ), anxiety (STAI-T) average weekly pain (VAS), pain variability (maximum-minimum average weekly pain), pain drawing (number of painful areas), and pressure pain sensitivity (P50).
*Significant at $P < .05$.

Questionnaire; $P = .001$), average weekly pain intensity (VAS; $P = .001$), and pain drawing ($P = .003$), but not for P50 ($P = .865$). Conversely, placebo nonresponders did not improve in any outcomes; FM effect ($P = .160$), average weekly pain intensity ($P = .495$), pain drawing ($P = .780$), or P50 ($P = .485$; Table 2). This provided validation that the general PGIC categorization of responders and nonresponders was consistently reflected in our pain-specific outcome measures.

The Effect of FM Duration on P50 at Baseline

A correlation analysis between age and FM duration revealed that the 2 variables were independent, in the placebo responder group, $r_{13} = .331$, $P = .228$, as well as in the placebo nonresponder group, $r_{20} = .299$, $P = .176$. This means that long FM durations were not only present in older patients, and short durations not only present in the younger patients, and our subsequent analyses of FM duration would thus not be confounded by age.

Among nonresponders there was a negative correlation between FM duration and baseline P50, $r_{20} = -.496$, $P = .019$, but not among responders $r_{13} = -.318$, $P = .248$; Fig 1). Across groups, there was no baseline correlation between FM duration and P50, $r_{35} = -.178$, $P = .292$.

The Effect of FM Duration on P50 Change From Baseline to After Treatment

Across groups, there was no significant correlation between FM duration and the primary outcome measure, defined as the mean change in P50 from baseline to after treatment, $r_{35} = .040$, $P = .816$. However, there was a significant negative correlation between FM duration and mean change in P50 among placebo responders $r_{13} = -.689$, $P = .004$, indicating that longer FM duration was associated with lower placebo-induced reductions in pain sensitivity. There was no significant association between FM duration and treatment responses among nonresponders $r_{20} = .348$, $P = .112$ (Fig 2). To control for the possible influence of depression (BDI) and catastrophizing (CSQ) scores on the results, we performed partial correlations between FM duration and P50, controlling for BDI and CSQ. Using partial correlations, we found the same results (ie, there was a significant correlation between FM duration and mean change in P50 among placebo responders; $r_{(13)} = .603$, $P = .029$, but not among non-responders $r(20) = -.376$, $P = .102$.

The Relationship Between FM Duration and Pain Symptom Variability

The variability of patients' weekly pain symptoms did not differ between groups at baseline ($P = .143$; Table 1). There was an overall correlation between pain variability and FM duration, indicating that variability in pain symptoms decrease over time in favor of more constant weekly pain levels, $r_{35} = -.345$, $P = .037$. In separate correlations for placebo responders and nonresponders, this negative correlation was seen among nonresponders, $r_{20} = -.480$, $P = .024$, but not among placebo responders, $r_{13} = -.070$, $P = .805$ (Fig 3).

Discussion

In this study we showed that placebo responses among FM patients were affected by the duration of chronic widespread pain. In line with previous evidence for neural plasticity in response to chronic pain exposure,[1,31,35,36,40] we found that the response to placebo treatment was reduced as a function of FM duration. Pain relief in response to placebo treatment has been widely investigated in healthy individuals, and involves activation of pain inhibitory circuitry in the brain and endogenous release of opioids.[10,44] Because FM is characterized by impaired function of the brain's pain inhibitory system, placebo analgesia may seem paradoxical. However, 2 comprehensive meta-analyses of placebo responses in FM clinical trials[17,18] confirm the presence of placebo responses in FM, even if

Table 2. Change From Baseline to After 12 Weeks of Placebo Treatment

	Overall Diff From Baseline to After	*Non-R at Baseline*	*Non-R After*	*Diff Non-R From Baseline to After*	*Diff Non-R P*	*Resp Baseline*	*Resp After*	*Diff in Resp From Baseline to After*	*Diff Resp P*	*Non-R Versus Resp P*
FIQ	9.75 ± 15.82	65.90 ± 11.91	62.95 ± 14.25	2.94 ± 9.47	.160	62.21 ± 19.31	42.46 ± 23.36	19.74 ± 18.14	.001*	.001*
Average weekly pain (VAS)	13.08 ± 20.76	67.84 ± 14.63	64.55 ± 17.14	3.50 ± 27.13		67.53 ± 14.58	40.40 ± 20.11	17.93 ± 16.44	.001*	<.001*
Pain variability	44.76 ± 20.61	41.4 ± 21.40	42.82 ± 18.82	1.40 ± 15.40	.570	49.67 ± 19.05	41.33 ± 18.57	8.33 ± 23.62	.155	.867
Pain-drawing	1.16 ± 2.77	8.46 ± 2.12	8.64 ± 1.46	1.00 ± 1.51	.780	8.33 ± 2.32	5.33 ± 3.46	3.0 ± 3.21	.003*	<.001*
P50	44.45 ± 215.31	418.70 ± 147.15	462.60 ± 220.38	43.90 ± 232.24	.485	361.80 ± 142.58	407.10 ± 187.8	45.27 ± 195.7	.865	.841

Abbreviations: Diff, difference; Non-R, nonresponder; Resp, responder.
NOTE. Data are presented as mean ± SD except where otherwise noted. Pain variability indicates maximum-minimum average weekly pain and pain-drawing, number of painful areas.
*Significant at $P < .005$.

Figure 1. Baseline correlation between FM duration and pain sensitivity. Correlations between FM duration (duration of widespread pain; months) and baseline pressure pain sensitivity (P50) among placebo nonresponders ($r_{20} = -.496$, $P = .019$) and placebo responders ($r_{13} = -.318$, $P = .248$).

responses were lower in FM compared with patients with peripheral neuropathy.[17]

The mechanisms responsible for placebo analgesia in FM are not well understood. In healthy subjects, brain areas rich in opioid receptors, such as the rACC have been implicated in placebo analgesia.[37] Compared with healthy subjects, reduced pain-related activation of the rACC[20] and lower functional connectivity between the rACC and other parts of the pain inhibitory network[21] have been documented in FM patients. FM patients also had reduced rACC volumes in relation to the duration of FM.[23] Furthermore, FM patients had lower mu-opioid receptor binding potential (MOR BP) compared with healthy control participants in brain areas implicated in pain inhibitory networks and placebo analgesia, including the rACC.[16] Recently, Schrepf et al[41] observed strong within-FM patients associations between MOR BP and cerebral pain-related activations in the rACC, posterior cingulate cortex (PCC), and medial frontal gyrus, which were related to pain intensity (ie, lower MOR BP was associated with weaker pain-related brain activations and higher pain ratings). In our previous study, specifically comparing milnacipran with placebo responders, we found segregated neural mechanisms for the positive response in FM patients.[22] After treatment, milnacipran responders exhibited significantly increased pain-related activation of the PCC, associated with reduced pain sensitivity (increased P50) and lower intensities of ongoing pain, whereas placebo responders did not exhibit increased PCC activation, nor, as reported in the present study, reduced pain sensitivity. However, both groups had increased pain-related activation of the amygdala after treatment. The amygdala has been associated with cannabinoid analgesia mediating the reduction of unpleasantness of ongoing pain, but not reduced pain sensitivity.[33] Thus, our previous functional magnetic resonance imaging results would indicate that the placebo response associated with clinical improvement in our FM cohort could involve endocannabinoid or possibly dopaminergic mechanisms, both

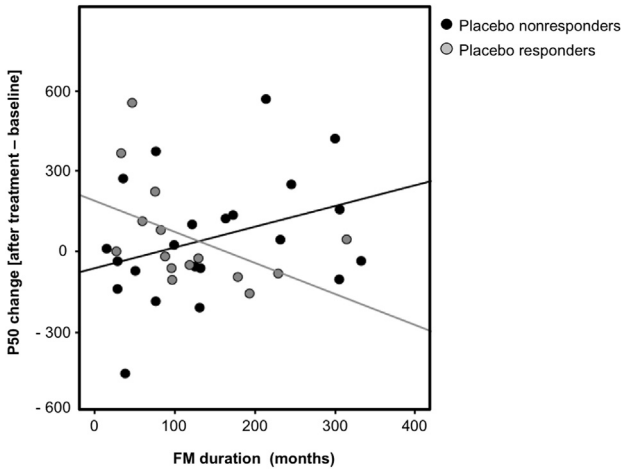

Figure 2. Correlation between FM duration and P50 change. Correlations between FM duration (duration of widespread pain; months) and change in pressure pain sensitivity (P50) from baseline to after treatment among placebo nonresponders (r_{20} = −.348, P = .112) and placebo responders (r_{13} = .689, P = .004).

previously implicated in placebo analgesia,[11,24] rather than endogenous opioids. Hypothetically, these nonopioid mechanisms are less influenced by pain duration and therefore explain the presence of placebo responses also in FM patients with long disease duration.

We did not find any baseline group differences in pain sensitivity (P50) between placebo responders and nonresponders, which tallies our previous results.[22] The lack of statistically significant group differences could be explained by the large interindividual variability in pressure pain sensitivity, which has been reported also in healthy subjects.[29] Despite the lack of an overall significant increase in P50 within the placebo group, patients with shorter pain duration had larger reductions in pain sensitivity. These results are in accordance with our previous findings that short pain duration was a positive predictor for milnacipran response, associated with significant reductions in pain sensitivity (increased P50).[22] The findings would indicate differential mechanisms for placebo reductions in pain sensitivity, that are negatively influenced by pain duration and possibly more dependent on endogenous opioids, and the placebo response influencing the more emotional/cognitive aspects of clinical pain.

To our knowledge, this is the first study addressing the effect of chronification on placebo responses, by assessing the relationship between FM duration and placebo analgesia. As mentioned, a previous study from our group showed significant neural plasticity in relation to FM duration, including cerebral atrophy in pain inhibitory regions,[23] indicating that time would likely be a key variable when assessing FM treatment mechanisms. The present results suggest that FM duration influences endogenous pain regulation, because placebo responses were negatively affected in the placebo arm of a randomized double-blinded clinical trial.

A partial correlation, controlling for depression and catastrophizing, confirmed that the relationship between FM duration and treatment outcome was not explained by differences in negative affect. Because the primary outcome of this trial gave different results if FM duration was not taken into account, our results point to the importance of taking pain duration into consideration when interpreting results from FM clinical trials, and possibly trials in other chronic pain conditions too. Even if our study included patients already diagnosed with FM, our results indicate that clinical interventions that depend on endogenous pain regulation may still be harnessed, and chronification avoided, if initiated early after chronic pain onset. In other words, our study has generated hypotheses around early prevention of FM, by illustrating a potential relationship between early FM and stronger endogenous pain modulation.

The present study represents a combination of a traditional drug trial and a mechanistic experimental study, in

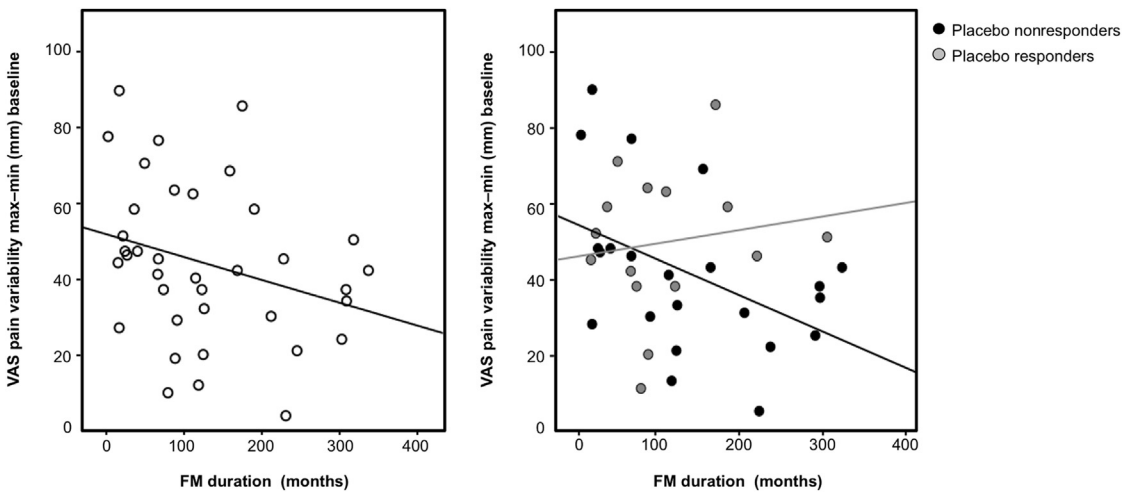

Figure 3. Baseline correlations between FM duration and pain variability. Left panel: correlation between FM duration and pain variability (maximum-minimum [max-min]) at baseline across placebo nonresponders and responders (r_{35} = −.345, P = .037). Right panel: correlation between FM duration and pain variability at baseline for placebo nonresponders (r_{20} = −.480, P = .024) and placebo responders (r_{13} = −.070, P = .805).

which the benefit of using a highly controlled treatment protocol is combined with the advantage of obtaining quantitative sensory data. Moreover, all patients were washed out of medications, which is not feasible in most experimental studies.

In this study we found that placebo responders had lower ratings of depression at baseline compared with nonresponders, and less catastrophizing thoughts (even if depression and catastrophizing had no effect on analyses regarding FM duration). The notion of predicting who will be a placebo responder has intrigued researchers and pharmaceutical companies since the recognition of placebo effects in medicine,[40] yet, there has been no conclusive evidence for a typical placebo responder.[26] In our study, patients with less negative affect at baseline were more likely to be placebo responders, perhaps because they were more likely to form positive expectations about the treatment. Placebo analgesia is closely related to expectations of pain relief and accounts for a large amount of variance in placebo responses.[6,43] Because the contextual factors are likely to vary considerably between trials, and treatment expectations may vary accordingly (ie, through differences in patient-clinician relationships)[27,28] it is unlikely that baseline depression and catastrophizing will always be associated with placebo responses. However, if negative affect has a negative influence on the general perception of the credibility of a clinical trial, this may affect placebo outcomes. In contrast to the baseline predictors for placebo responses in FM in this study (depression and catastrophizing), our previous study revealed that predictors of the response to milnacipran (a serotonergic/noradrenergic drug) was independent of psychological variables.[22]

An overall correlation showed that weekly pain levels were less variable over time, leading to more constant pain (in line with previous research suggesting that FM patients are less sensitive to variations in weather with time[13]). Placebo responders, however, did not show the same transition toward more constant pain levels with longer FM duration. Hence, the overall relationship between less variable pain and FM duration was driven by nonresponders. It is possible that a variable pain profile is favorable for recruiting endogenous pain responses, because pain may still be malleable, in contrast to patients with a less flexible pain modulatory system. It is our hope that future pain studies will include pain variability as a study variable when assessing response to treatment and factors for individualizing treatment.

Future Studies and Emerging Hypotheses

A recent meta-analysis[9] presented a statistical synthesis of 37 FM neuroimaging studies published before March 2015. The meta-analysis validates the idea of a dysfunction of the descending pain modulatory system in FM, because there was hypoactivity in the subgenual anterior cingulate cortex and the amygdala, together with hyperactivation of the insula. Because the same regions are implicated in placebo analgesia, it seems reasonable that placebo responses decrease over time with FM pain. However, a small experimental study of spinal withdrawal reflexes in FM[14] suggests segregation between cerebral and spinal processes during expectancy-driven analgesia; indicating that descending pain inhibition failed to affect spinal activity. Thus, there is a possibility that expectancy-induced pain relief is differently represented in FM patients, due to constant spinal hyperexcitability. As in most other studies, the study on spinal reflexes did not analyze results in relation to FM duration, and patients were not washed out of medications (opiates, tricyclics, antiepileptic drugs, etc, were taken). In future studies, the inclusion of pain duration in analyses of chronic pain will provide a better understanding of possible routes to pain relief. Recent studies have shown clear evidence of neural plasticity in several common pain disorders over time, including FM, and the search for chronic pain treatment should reflect that knowledge by taking time since pain onset into account. It is our hope that future studies will have a dynamic perspective on patients on the basis of pain duration, rather than a binary classifier of "healthy" or "diseased."

Limitations

The present study used a traditional placebo-controlled design, and did not include a natural history control group. This means that the placebo responses could not be controlled for general factors such as spontaneous remission or regression to the mean. However, long-term follow-up of FM patients indicate small chances of recovery.[4,12] Another limitation is the small sample. The present study was a secondary analysis of a randomized controlled trial aimed at comparing pain mechanisms in response to treatment with milnacipran (n = 46) and placebo (n = 46). Hence, the power in the original study was adequate, but in the present subgrouping into placebo responders and nonresponders we have poorer power, which restricted the type of analyses we could perform. In a larger study, regression analyses could have provided sophisticated models of the contribution of different factors to placebo responses. Despite the small sample size, we hope that the present study can be seen as a first indication of a new line of studies that take pain duration into consideration when studying the effects of treatments for chronic pain.

References

1. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR: Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci 24:10410-10415, 2004

2. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, Apkarian AV: Chronic pain and the emotional

brain: Specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 26:12165-12173, 2006

3. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J: An inventory for measuring depression. Arch Gen Psychiatry 4: 561-571, 1961

4. Bengtsson A, Bäckman E, Lindblom B, Skogh T: Long term follow-up of fibromyalgia patients. J Musculoskelet Pain 2: 67-80, 1994

5. Bingel U, Lorenz J, Schoell E, Weiller C, Buchel C: Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 120:8-15, 2006

6. Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, Tracey I: The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med 3:70ra14, 2011

7. Burckhardt CS, Clark SR, Bennett RM: The fibromyalgia impact questionnaire: Development and validation. J Rheumatol 18:728-733, 1991

8. Burckhardt CS, Henriksson C: The Coping Strategies Questionnaire – Swedish version: Evidence of reliability and validity in patients with fibromyalgia. Scand J Behav Ther 30: 97-107, 2001

9. Dehghan M, Schmidt-Wilcke T, Pfleiderer B, Eickhoff SB, Petzke F, Harris RE, Montoya P, Burgmer M: Coordinate-based (ALE) meta-analysis of brain activation in patients with fibromyalgia. Hum Brain Mapp 37:1749-1758, 2016

10. Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, Buchel C: Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron 63: 533-543, 2009

11. Ellingsen DM, Wessberg J, Eikemo M, Liljencrantz J, Endestad T, Olausson H, Leknes S: Placebo improves pleasure and pain through opposite modulation of sensory processing. Proc Natl Acad Sci U S A 110:17993-17998, 2013

12. Fors EA, Landmark T, Bakke O: Contextual and time dependent pain in fibromyalgia: An explorative study. BMC Res Notes 5:644, 2012

13. Fors EA, Sexton H: Weather and the pain in fibromyalgia: Are they related? Ann Rheum Dis 61:247-250, 2002

14. Goffaux P, de Souza JB, Potvin S, Marchand S: Pain relief through expectation supersedes descending inhibitory deficits in fibromyalgia patients. Pain 145:18-23, 2009

15. Gracely RH, Petzke F, Wolf JM, Clauw DJ: Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 46:1333-1343, 2002

16. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK: Decreased central mu-opioid receptor availability in fibromyalgia. J Neurosci 27:10000-10006, 2007

17. Hauser W, Bartram-Wunn E, Bartram C, Reinecke H, Tolle T: Systematic review: Placebo response in drug trials of fibromyalgia syndrome and painful peripheral diabetic neuropathy-magnitude and patient-related predictors. Pain 152:1709-1717, 2011

18. Hauser W, Sarzi-Puttini P, Tolle TR, Wolfe F: Placebo and nocebo responses in randomised controlled trials of drugs applying for approval for fibromyalgia syndrome treatment: Systematic review and meta-analysis. Clin Exp Rheumatol 30: 78-87, 2012

19. Hurst H, Bolton J: Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 27:26-35, 2004

20. Jensen KB, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Giesecke T, Mainguy Y, Gracely R, Ingvar M: Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. Pain 144:95-100, 2009

21. Jensen KB, Loitoile R, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Mainguy Y, Vitton O, Gracely RH, Gollub R, Ingvar M, Kong J: Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. Mol Pain 8:32, 2012

22. Jensen KB, Petzke F, Carville S, Choy E, Fransson P, Gracely RH, Vitton O, Marcus H, Williams SC, Ingvar M, Kosek E: Segregating the cerebral mechanisms of antidepressants and placebo in fibromyalgia. J Pain 15: 1328-1337, 2014

23. Jensen KB, Srinivasan P, Spaeth R, Tan Y, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Vitton O, Gracely R, Ingvar M, Kong J: Overlapping structural and functional brain changes in patients with long-term exposure to fibromyalgia pain. Arthritis Rheum 65:3293-3303, 2013

24. Jubb J, Bensing JM: The sweetest pill to swallow: How patient neurobiology can be harnessed to maximise placebo effects. Neurosci Biobehav Rev 37:2709-2720, 2013

25. Julien N, Goffaux P, Arsenault P, Marchand S: Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 114:295-302, 2005

26. Kaptchuk TJ, Kelley JM, Deykin A, Wayne PM, Lasagna LC, Epstein IO, Kirsch I, Wechsler ME: Do "placebo responders" exist? Contemp Clin Trials 29:587-595, 2008

27. Kelley JM, Kraft-Todd G, Schapira L, Kossowsky J, Riess H: The influence of the patient-clinician relationship on healthcare outcomes: A systematic review and meta-analysis of randomized controlled trials. PLoS One 9: e94207, 2014

28. Kong J, Spaeth R, Cook A, Kirsch I, Claggett B, Vangel M, Gollub RL, Smoller JW, Kaptchuk TJ: Are all placebo effects equal? Placebo pills, sham acupuncture, cue conditioning and their association. PLoS One 8:e67485, 2013

29. Kosek E, Ekholm J, Nordemar R: A comparison of pressure pain thresholds in different tissues and body regions. Long-term reliability of pressure algometry in healthy volunteers. Scand J Rehabil Med 25:117-124, 1993

30. Kosek E, Hansson P: Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain 70:41-51, 1997

31. Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC: Accelerated brain gray matter loss in fibromyalgia patients: Premature aging of the brain? J Neurosci 27:4004-4007, 2007

32. Lautenbacher S, Rollman GB: Possible deficiencies of pain modulation in fibromyalgia. Clin J Pain 13:189-196, 1997

33. Lee MC, Ploner M, Wiech K, Bingel U, Wanigasekera V, Brooks J, Menon DK, Tracey I: Amygdala activity contributes to the dissociative effect of cannabis on pain perception. Pain 154:124-134, 2013

34. Levine JD, Gordon NC, Fields HL: The mechanism of placebo analgesia. Lancet 2:654-657, 1978

35. Lutz J, Jager L, de Quervain D, Krauseneck T, Padberg F, Wichnalek M, Beyer A, Stahl R, Zirngibl B, Morhard D, Reiser M, Schelling G: White and gray matter abnormalities in the brain of patients with fibromyalgia: A diffusion-tensor and volumetric imaging study. Arthritis Rheum 58: 3960-3969, 2008

36. Obermann M, Nebel K, Schumann C, Holle D, Gizewski ER, Maschke M, Goadsby PJ, Diener HC, Katsarava Z: Gray matter changes related to chronic posttraumatic headache. Neurology 73:978-983, 2009

37. Petrovic P, Kalso E, Petersson KM, Ingvar M: Placebo and opioid analgesia– imaging a shared neuronal network. Science 295:1737-1740, 2002

38. Petzke F, Jensen KB, Kosek E, Choy E, Carville S, Fransson P, Williams SCR, Marcus H, Mainguy Y, Ingvar M, Gracely RH: Using fMRI to evaluate the effects of milnacipran on central pain processing in patients with fibromyalgia. Scand J Pain 4:65-74, 2013

39. Rampakakis E, Ste-Marie PA, Sampalis JS, Karellis A, Shir Y, Fitzcharles MA: Real-life assessment of the validity of Patient Global Impression of Change in fibromyalgia. RMD Open 1:e000146, 2015

40. Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A: Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. J Neurosci 29: 13746-13750, 2009

41. Schrepf A, Harper DE, Harte SE, Wang H, Ichesco E, Hampson JP, Zubieta JK, Clauw DJ, Harris RE: Endogenous opioidergic dysregulation of pain in fibromyalgia: A PET and fMRI study. Pain 157:2217-2225, 2016

42. Spielberger CD: Manual For The State-Trait Anxiety Inventory (Form Y). Palo Alto, CA, Consulting Psychologists Press, 1983

43. Vase L, Robinson ME, Verne NG, Price DD: The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. Pain 105:17-25, 2003

44. Wager TD, Atlas LY: The neuroscience of placebo effects: Connecting context, learning and health. Nat Rev Neurosci 16:403-418, 2015

45. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD: Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 303:1162-1167, 2004

46. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473-483, 1992

47. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lightbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell AJ, Sheon RP: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 33:160-172, 1990

48. Zubieta JK, Bueller JA, Jackson LR, Scott DJ, Xu Y, Koeppe RA, Nichols TE, Stohler CS: Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. J Neurosci 25:7754-7762, 2005