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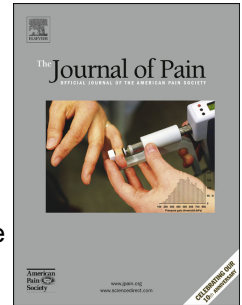
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Lower placebo responses after long-term exposure to fibromyalgia pain

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Abstract

Knowledge about placebo mechanisms in patients with chronic pain is scarce. Fibromyalgia syndrome (FM) is associated with dysfunctions of central pain inhibition, and since placebo analgesia entails activation of endogenous pain inhibition, we hypothesized that long-term exposure to FM pain would negatively affect placebo responses. Here 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. 22 patients were classified as placebo non-responders and 15 as responders, according to the Patient Global Impression of Change (PGIC) scale. Primary outcome was the change in pressure pain sensitivity from baseline to post-treatment. Secondary outcomes included ratings of clinical pain (VAS), FM impact (FIQ) and pain drawing. Among placebo responders, longer FM duration was associated with smaller reductions in pressure pain sensitivity (r=0.689, p=.004), but not among non-responders (r=-0.348, p=.112). Here, we demonstrate that FM duration influences endogenous pain regulation, as pain levels and placebo-induced analgesia were negatively affected. Our results point to the importance of early FM interventions, as endogenous pain regulation may still be harnessed at that early time. Also, placebo-controlled trials should take FM duration into consideration when interpreting results. Clinical trial registration EudraCT 2004-004249-16.

Introduction

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 (e.g. 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, 44] and endogenous release of opioids in the brain [48].

Since 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, where 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 to patients with neuropathy who are not characterized by central disinhibition [17]. Yet, there was presence of some degree of placebo responses among FM patients [17, 18], and as 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 demonstrated 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 grey 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 which 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.

Here, we investigate 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. In order to address this question, we used the placebo data from a double-blind, randomized, placebo-controlled clinical trial where patients were treated with the selective Noradrenalin Serotonin Re-uptake Inhibitor (SNRI) milnacipran, or placebo.

Methods

Patients

A total of 92 patients were randomized and included in the overall clinical trial, whereof 46 were randomized to the placebo arm. Outcome data from 38 patients in the placebo group was available after treatment, yet one patient was excluded from the statistical analyses due to *en passant* neurological findings. Hence, all statistics are based on 37 patients. Results from the overall clinical trial can be found in previous publications.[22,38]. Patients eligible for inclusion were females, aged 18–55 years, fulfilling the ACR 1990 criteria for FM [47] and with

a self reported average weekly pain intensity of at least 40 mm on a 100 mm visual analogue 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 ECG abnormalities and hypertension), liver disease, renal impairment, pregnancy or breastfeeding. Therapies that could interfere with the tested treatment were prohibited; i.e., 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 (TENS). Paracetamol and dipyrone were allowed as rescue medicines and short-term use of zolpidem was allowed as treatment for insomnia. Nonsteroidal anti-inflammatory drugs (NSAIDs) were allowed under control from the study investigators. Rescue medications and NSAIDs had to be discontinued 48 hours prior to assessments of symptoms and pain sensitivity. This study was approved by the local ethical committee at each site, and informed consent was obtained before inclusion. Initial information about the study was given to patients over 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. Initial information about the study was given to patients over 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

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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 treatment with milnacipran or placebo (EudraCT no. 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 7-28 days prior to study inclusion and consisted of a clinical examination, questionnaires and laboratory tests in order to confirm eligibility. A second visit (baseline visit) was scheduled following at least 7 days, or the time needed for medication wash-out. During the second visit, baseline assessments were performed. The following day, patients returned for a brain scan and then started the treatment (milnacipran/placebo). Following a three weeks dose escalation, patients had a nine-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

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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 (i.e. PGIC 1, 2 or 3). Non-responders were defined as patients having no change (i.e. PGIC 4) or worsening of symptoms (i.e. 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

In order 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's Depression Inventory, BDI) [3], anxiety (Spielberger State Trait Anxiety Inventory, STAI-T) [42], catastrophizing thoughts (subscale of the Coping Strategies Questionnaire, CSQ) [8] and general health (complete SF-36, combination of mental and physical component) [45].

Primary outcome – pressure pain sensitivity (P50)

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 $1cm^2$ probe [20]. Patients were assessed for pressure pain sensitivity by receiving one ascending series of pressure stimuli and one randomized series. Pain intensity in response to each stimulus was rated on a 100 mm Visual Analogue Scale (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, based on 15 randomized stimuli in the range between each patient's pain threshold and the first pressure that exceeded VAS 60 mm. The

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polynomial regression was used because the relationship between stimulus (pressure) and response (pain ratings) had non-linear 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 (max-min) (VAS 0-100 mm) at baseline; average weekly pain intensity (VAS); number of painful areas (pain drawing); impact of FM symptoms (Fibromyalgia Impact Questionnaire, FIQ) [7].

Statistical analyses

Differences at baseline, and differences from baseline to after treatment, were analyzed using one sample t-tests (within groups) and independent samples t-tests (between groups). Due to 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's r coefficient (when ordinal measures were included), except for the correlation between FM duration and age, which was analyzed with Pearson's *r* (continuous measures). All statistical analyses were performed in SPSS 23.0. The significance level was set as $p < 0.05$, two-tailed.

Results

Patient characteristics

Among all patients in the placebo arm of this clinical trial, 22 patients were non-responders and 15 were responders according to the PGIC measure. The mean age across responders and non-responders 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 non-responders

Placebo responders had lower ratings of depression (BDI) at baseline compared to non-responders ($p=0.015$), and less catastrophizing thoughts (CSQ) ($p=0.021$). No significant differences were found in any other baseline variables between the groups (Table 1).

== Table 1 ==

Change from baseline to after treatment for placebo responders and non-responders

Patients who reported a positive treatment response on PGIC were significantly improved in almost all outcomes measures from before treatment to after treatment, including FM impact (FIQ; $p=0.001$), average weekly pain intensity (VAS; $p=0.001$) and pain drawing ($p=0.003$), but not for P50 ($p=0.865$). Conversely, placebo non-responders did not improve in any outcomes; FM impact ($p=0.160$), average weekly pain intensity ($p=0.495$), pain drawing ($p=0.780$) or P50 ($p=0.485$) (Table 2). This provided validation that the general PGIC categorization of responders and non-responders was consistently reflected in our pain-specific outcome measures.

== Table 2 ==

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The effect of FM duration on P50 - Baseline

A correlation analysis between age and FM duration revealed that the two variables were independent, both in the placebo responder group, $r(13)=0.331$, p=0.228, and the placebo non-responder group, $r(20)=0.299$, p=0.176. This means that long FM durations were not only present in older patients, and short durations not only present in the younger, and our subsequent analyses of FM duration would thus not be confounded by age.

Among non-responders there was a negative correlation between FM duration and baseline P50, $r(20)=-0.496$, $p=0.019$, but not among responders $r(13)=-0.318$, $p=0.248$) (see Figure 1). Across groups, there was no baseline correlation between FM duration and P50, $r(35)=-0.178$, $p=0.292$.

== Figure 1 ==

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, $r(35)=0.040$, $p=0.816$. Yet, there was a significant negative correlation between FM duration and mean change in P50 among placebo responders $r(13)=-.689$, $p=0.004$, 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 non-responders $r(20)=.348$, $p=0.112$, (Figure 2). In order 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, i.e. there was a significant correlation between FM duration and mean change in P50 among placebo responders $r(13)=0.603$, $p=0.029$, but not among non-responders $r(20)=-0.376$, $p=0.102$.

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== Figure 2 ==

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, $r(35)$=-0.345, p=0.037. In separate correlations for placebo responders and non-responders, this negative correlation was seen among non-responders $r(20)$=-0.480, p=0.024, but not among placebo responders $r(13)$=-0.070, p=0.805 (Figure 3).

== Figure 3 ==

Discussion

Here we demonstrate that placebo responses among FM patients in our study 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, 43]. Since FM is characterized by impaired function of the brain's pain inhibitory system, placebo analgesia may seem paradoxical. Yet, two comprehensive meta-analyses of placebo responses in FM clinical trials [17, 18] confirm the presence of placebo responses in FM, even if responses were lower in FM compared to 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 rostral anterior cingulate cortex (rACC) have been implicated in placebo analgesia [37]. Compared to healthy subjects,

reduced pain related activation of 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 my opioid receptor binding potential (MOR BP) compared to healthy controls in brain areas implicated in pain inhibitory networks and placebo analgesia, including rACC [16]. Recently, Scherpf et al. [41] observed strong within-FM patients associations between MOR BP and cerebral pain related activations in rACC, PCC and medial frontal gyrus, which were related to pain intensity, i.e., lower MOR BP were 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]. Following treatment, milnacipran responders exhibited significantly increased pain related activation of 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 sudy, reduced pain sensitivity. However, both groups had increased pain related activation of the amygdala following treatment. Amygdala has been associated with cannabinoid analgesia mediating the reduction of unpleasantness of ongoing pain, but not reduced pain sensitivity [33]. Thus, our previous fMRI results would indicate that the placebo response associated with clinical improvement in our FM cohort could involve endocannabinoid or possibly dopaminergic mechanisms, both previously implicated in placebo analgesia [11, 24], rather than endogenous opioids. Hypothetically, these non-opioid 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 non-responders, which tallies our previous results [22]. The lack of statistically

significant group differences could be explained by the large inter-individual 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 impact of chronification on placebo responses, by assessing the relationship between FM duration and placebo analgesia. As mentioned, a previous study from our group demonstrated 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, as 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. As 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

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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, where 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 to non-responders, and less catastrophizing thoughts (even if depression and catastrophizing had no impact 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, 46]. As the contextual factors are likely to vary considerably between trials, and treatment expectations may vary accordingly (i.e. through differences in patient-clinician relationship) [27, 28], it is unlikely that baseline depression and catastrophizing will always be associated with placebo responses. Yet, if negative affect has a negative influence on the general perception of the credibility of a clinical trial, this may impact placebo outcomes. In contrast to the baseline predictors for placebo responses in FM reported here (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 display the same transition towards more constant pain levels with longer FM duration. Hence, the overall relationship between less variable pain and FM duration was driven by non-responders. It is possible that a variable pain profile is favorable for recruiting endogenous pain responses, as 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, as there was hypoactivity in the subgenual anterior cingulate cortex and the amygdala, together with hyperactivation of the insula. As the same regions are implicated in placebo analgesia, it seems reasonable that placebo responses decrease over time with FM pain. Yet, 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 analyse 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 demonstrated 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 based on 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. Yet, 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 RCT 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 non-responders 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. In spite of 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.

Disclosures

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Figure legends

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 non-responders ($r(20)$=-0.496, p=0.019) and placebo responders ($r(13)$=-0.318, p=0.248).

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 non-responders ($r(20)$=-0.348, p=0.112) and placebo responders ($r(13)$=0.689, p=0.004).

Figure 3. Baseline correlations between FM duration and pain variability. Left panel: Correlation between FM duration and pain variability (max-min) at baseline across placebo non-responders and responders *($r(35)$=-0.345, p=0.037)*. Right panel: Correlation between FM duration and pain variability at baseline for placebo non-responders ($r(20)$=-0.480, p=0.024) and placebo responders ($r(13)$=-0.070, p=0.805).

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Table 1. Baseline characteristics (mean ± SD). Age (years), FM duration (months), ratings of depression (BDI), catastrophizing (CSQ), general health (SF36), fibromyalgia impact (FIQ), anxiety (STAI-T) average weekly pain (VAS), pain variability (max-min average weekly pain), pain drawing (number of painful areas) and pressure pain sensitivity (P50).

	Total n=37	Non-responders n=22	Responders n=15	Difference (p-value)
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*
SF36	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

Table 2. **Change (mean ± SD) from baseline to after 12 weeks of placebo treatment.** Non-Responders='Non-R' and Responders='Resp'. Fibromyalgia impact (FIQ), average weekly pain (VAS), pain variability (max-min average weekly pain), pain drawing (number of painful areas) and pressure pain sensitivity (P50).

	Overall Diff Baseline /after	Non-R Baseline	Non-R After	Diff Non-R Baseline /after	Diff Non-R p-value	Resp Baseline	Resp After	Diff Resp Baseline/ after	Diff Resp p-value	Non-R vs. Resp p-value
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

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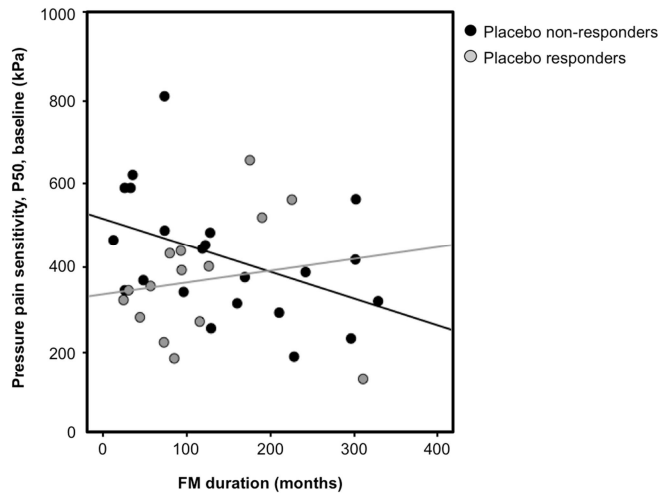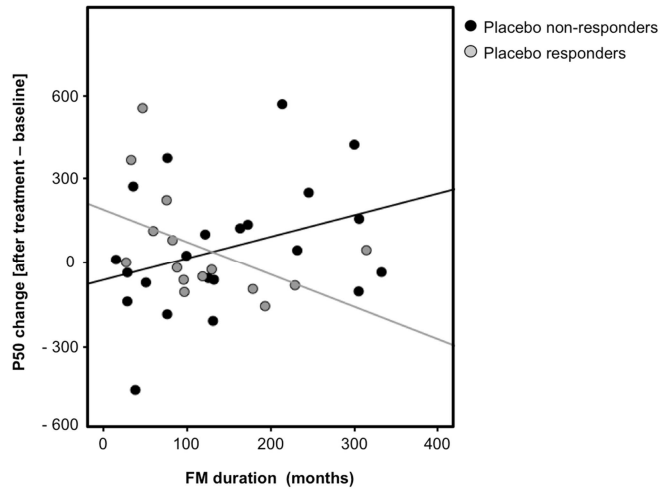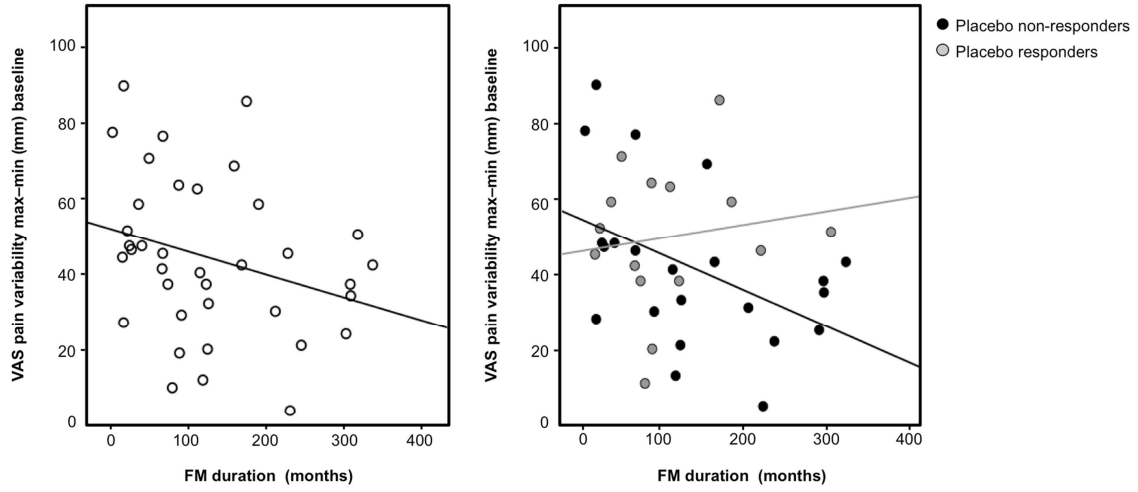
HIGHLIGHTS

- Long-term exposure to fibromyalgia was associated with lower placebo analgesia
- Subjective report of placebo response correlated with clinical improvements
- Placebo responders had lower ratings of depression symptoms at baseline