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Occipital Nerve Stimulation in Fibromyalgia: A Double-Blind Placebo-Controlled Pilot Study With a Six-Month Follow-Up

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Objective: The goal of this study is to evaluate the effectiveness of occipital nerve stimulation (ONS) as a surgical treatment for fibromyalgia in a placebo-controlled design.

Materials and Methods: Eleven patients were selected based on the American College of Rheumatology-90 criteria and implanted with an occipital nerve trial-lead stimulator. Baseline scores for pain, mood, and fatigue were acquired, and patients were randomized in a ten-week double-blinded crossover design with placebo and effective subsensory threshold stimulation (no paresthesias). After finalizing the trial, nine patients were implanted permanently; evaluation was performed prior to surgery and at six months after surgery for pain, fatigue, and mood of the number of trigger points and overall morbidity.

Results: Significant results were found during the trial for a decrease in pain intensity (39.74%) on visual analogue scale (VAS; $p < 0.001$) and pain catastrophizing scale (PCS) during effective stimulation. A total of 9/11 patients responded to trial treatment; however, in two patients, this might be a placebo effect, recognizable due to the study design. Six months after permanent implantation, pain intensity remained decreased (44.01%) on VAS ($p < 0.05$). Besides the VAS, significant changes were noted for PCS, fatigue (modified fatigue impact scale), the number of trigger points, and overall morbidity (fibromyalgia impact questionnaire). There were no serious adverse events.

Conclusions: Our data strongly suggest that ONS is beneficial in the treatment of fibromyalgia. The beneficial effects are stable at six months after permanent implantation. Subsensory threshold stimulation is feasible in designing a placebo-controlled trial.

Keywords: Fibromyalgia, greater occipital nerve stimulation, placebo controlled, six months, subthreshold

Conflict of Interest: Mark Plazier and Dirk De Ridder are involved in paid educational tasks for St. Jude Medical Neuromodulation (Plano, TX, USA). The other authors reported no conflicts of interest.

INTRODUCTION

Fibromyalgia is characterized by widespread musculoskeletal pain. The diagnostic criteria, proposed by the American College of Rheumatology (ACR), comprise of a history of widespread pain, affecting all four quadrants of the body, lasting for minimally three months. Furthermore, 11 out of 18 designated tender points should elicit pain when applying 4 kg of pressure (1). Pain is often accompanied by sleep disorders, fatigue, and headache, as well as psychological problems (2–4).

The prevalence is up to 2.9–4%, mainly affecting women in a 9:1 ratio. The mean age of onset is between 20 and 55 years (5–7). Fibromyalgia has a large financial impact on social healthcare costs, both on direct medical costs (treatment, patient care) and indirect costs (work loss). These costs are estimated at €7814 per person per year in Europe and at $9573 in the United States (7–9).

As fibromyalgia lacks a generally accepted pathophysiology, a myriad of treatments has been proposed, none of which that have a high success rate. The European League against Rheumatism and the American Pain Society formulated recommendations and evidence-based guidelines for its treatment (10,11). Treatment consists of pharmacological and nonpharmacological approaches (12,13). The implementation of antidepressant therapy (14,15) and novel treatment strategies with pregabaline and duloxetine may expand the therapeutic options (16–18).

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Table 1. Patients' Demographics and Baseline Scores.

Subject	Age (years)	YSO	YSD	VAS	PCS	BDI-II	PVAQ	mFIS
1	43	2	1	10	16	22	19	54
2	49	4	1	7	14	28	40	60
3	38	2	0	9	1	6	20	31
4	36	13	1	9	19	21	34	46
5	58	9	6	9	29	28	41	70
6	36	6	1	6	31	26	42	49
7	36	8	1	7	29	13	40	25
8	36	8	1	9	27	29	38	56
9	45	2	1	9	23	24	49	50
10	55	8	2	10	15	17	16	39
11	35	4	0	10	22	28	35	75
Mean	42 (35–58)	6 (2–13)	1 (1–6)	8.64 (6–10)	20.55 (1–31)	22.00 (6–29)	34.00 (16–49)	50.45 (25–75)

YSO, years since onset; YSD, years since diagnosis; VAS, visual analogue scale for fibromyalgia-associated pain (range 0–10); PCS, pain catastrophizing scale (range 0–52); PVAQ, pain vigilance and awareness questionnaire (range 0–80); BDI-II, Beck Depression Inventory 2nd edition (range 0–63); mFIS, modified fatigue impact scale (range 0–84).

Occipital nerve stimulation (ONS) is being successfully used as a surgical treatment for primary headache syndromes; however, there are no placebo-controlled studies (19). Recently, ONS was performed in patients who met criteria for fibromyalgia, presenting with comorbid headache disorder (20). In this specific study, which lacked placebo control as well, it was noted that not only headaches but also the widespread bodily pain improved. Furthermore, associated mood and fatigue scales improved.

The principal mechanism of peripheral nerve stimulation (PNS), including ONS, in the treatment of pain is based on the gate control theory (21). It is generally accepted that paresthesias are a mandatory by-product of PNS in order to be effective. Up until now, this had been a severe limitation for demonstrating its efficacy by precluding placebo-controlled trials (22). However, a recent unpublished functional magnetic resonance imaging study from the authors' group showed similar cerebral activations in both sub- and supra-sensory threshold stimulation. This allows for subthreshold (absence of paresthesias) studies to commence in order to control for the placebo response in pain trials, which can be up to 35% (23).

Based on these findings, the authors performed the first double-blind placebo-controlled crossover study using ONS in pain, more specifically in fibromyalgia, with a six-month follow-up.

PATIENTS AND METHODS

Selection of Patients

Patients suffering from fibromyalgia were selected by the Department of Physical Medicine and Rehabilitation at the University Hospital Antwerp, Belgium according to the criteria of the ACR-90 (1). Patients harboring pathologies mimicking the symptoms of fibromyalgia, as well as patients suffering from severe organic or psychiatric comorbidity (except minor depressive disorder), were excluded from participation. None of the patients were suffering from cervicotrigeminal tract radicular symptoms or types of hemicrania.

Eleven patients were included. All patients were of the female gender with a mean age of 42 years (42.45 ± 8.31 years, mean ± standard deviation [*SD*]) (Table 1). All patients were intractable to tryciclic antidepressants (amitryptiline), pain medication, magnesium supplements, physical therapy, and psychological support. All patients agreed to make no changes in their current medication intake, which primarily included aforementioned medication.

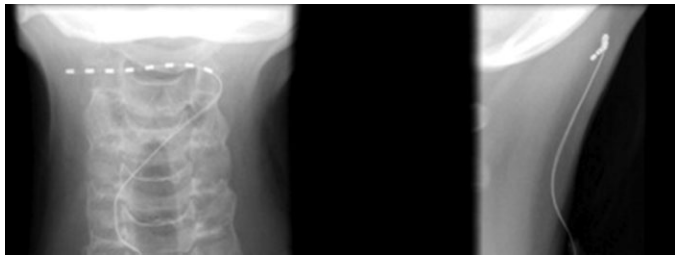

Figure 1. Anteroposterior and lateral radiographs of the location of the occipital electrode during trial implantation.

All patients gave written informed consent, and the ethical committee of the University Hospital Antwerp, Belgium approved the study.

Surgical Intervention

All patients were implanted on the same day with a subcutaneous occipital nerve stimulator under local anesthesia in prone position. An eight-contact trial wire (Octrode lead; St. Jude Medical, Plano, TX, USA) was inserted transversely crossing the midline of the occipital skin area just below the inion (Fig. 1).

One lead was inserted at the occipital subcutaneous skin area to cover both main branches of the greater occipital nerve. This technique was chosen because it was safer compared with high cervical spinal cord stimulation of C2 and less invasive.

Radiographic control verified the location of the electrode. The distal part of the lead was tunnelled subcutaneously in a sharp angle to prevent lead migration and externalized just below the hairline.

Patients were provided with an external multi trial stimulator (St. Jude Medical) preprogrammed with five different stimulation frequencies (6, 10, 12, 18, and 40 Hz). Pulse widths and polarities were fixed (300 μs; alternating positive and negative poles). During a one-week period, patients were able to test the five frequencies. The frequency that improved pain best was then selected for the cross-over trial period (Table 2).

Table 2. Settings Used for Occipital Nerve Stimulation During the Ten Week Crossover Period.

Subject	Frequency (Hz)	Pulse width (μs)	Amplitude (mA)	Pattern
1	40	300	1.0–1.5	Continuous
2	10	300	1.0–2.3	Continuous
3	40	300	0.5–1.7	Continuous
4	6	300	2.3–3.4	Continuous
5	12	300	1.2–2.0	Continuous
6	6	300	1.5–1.5	Continuous
7	6	300	1.8–3.9	Continuous
8	12	300	1.7–4.2	Continuous
9	18	300	1.2–1.2	Continuous
10	6	300	0.7–0.9	Continuous
11	12	300	0.8–1.0	Continuous

Frequencies were chosen after the one-week trial period based on best pain suppression. The amplitude indicates the individual range during effective stimulation. The subsensory threshold amplitude varied among time at the individual level; weekly determination of the sensory threshold prevented suprathreshold stimulation from interfering with placebo control.

After the trial period, all participating patients got the opportunity to get implanted with a permanent internal pulse generator (IPG). Nine patients chose to do so and underwent permanent implantation under general anesthesia according to the procedure described above. The old eight-contact trial wire Octrode lead was removed and replaced with a new eight-contact trial wire. Octrode lead was connected to an extension lead (St. Jude Medical), which was tunnelled subcutaneously to a pocket at the lower back (side according to preference of the patient). Subsequently, the distal part of the extension lead was connected to an IPG (EON, St. Jude Medical), which was placed in the subcutaneous pocket at the lower back. At least ten days was provided between the removal of the old eight-contact trial wire Octrode lead and the placement of a new lead.

Objectives and Outcome Parameters

Study objectives are to answer the three following questions: 1) What is the placebo-controlled effectiveness of ONS in fibromyalgia treatment? 2) What are the long-term results of stimulation? 3) Is placebo control in ONS feasible using subthreshold stimulation?

Subthreshold was defined as stimulation with amplitude just below paresthesia threshold level.

During the trial period of ten weeks, the effectiveness of stimulation was evaluated on a weekly basis with the following scales: 1) visual analogue scale (VAS, range 0–10) for fibromyalgia associated pain intensity; 2) pain catastrophizing scale (PCS) (24); 3) pain vigilance and awareness questionnaire (PVAQ) (25); 4) Beck Depression Inventory-II (BDI-II) (26); and 5) modified fatigue impact scale (mFIS) (27). Baseline scores were obtained in all patients prior to surgery (Table 1). The primary outcome parameter was a decrease on the VAS. The number of trigger points (TPs) eliciting pain was not evaluated on a weekly basis because the authors did not expect changes in such a short time window.

To evaluate the long-term effectiveness of stimulation, the same scales were applied, extended with the number of TPs and the Fibromyalgia Impact Questionnaire (FIQ) (28). Baseline scores were obtained prior to permanent implantation and follow-up scores at six months. (Table 4).

Study Design

During the trial period, the authors assigned the patients in an individually randomized double-blind crossover trial consisting of ten weeks. During these weeks, two stimulation sets were applied at random in an equal amount (Fig. 2). Either *effective* subthreshold stimulation (at the chosen maximally pain suppressive frequency) or *placebo* stimulation (stimulation at 0.10 mA) was applied. Stimulation at 0.10 mA was chosen due to technical limitations of the device. In order to have placebo stimulation, the patient should be capable of turning the device "on" and off. This is not possible at 0.00 mA; hence, the lowest amplitude possible was chosen to serve as the placebo parameter.

The threshold was verified systematically every week and was corrected for pressure application at the electrode location (to blind the patient for the stimulation design and to correct for intraindividual variability). This was performed by increasing the amplitude until sensory threshold and afterward carefully decreasing the amplitude until subsensory threshold. Subsequently, the stimulator got programmed according to the randomization. The stimulator could be turned on or off at will by the patient (Table 2).

Evaluation of the patients was performed weekly before progressing to the next stimulation situation.

A physician of the Neurosurgical Department (MP), who was blinded for the clinical evaluation, performed the programming. A physician of the Physical Medicine and Rehabilitation Department (IDK), who was blinded for the programming, performed the clinical evaluation. The patients were blinded for the stimulation situation during the ten weeks.

After permanent implantation, an open-label follow-up was performed with evaluation at six months (Fig. 2).

Statistical Methods

All analyses were performed with a statistical software (SPSS version 15.0, SPSS Inc., Chicago, IL, USA). In order to assess a time effect over the ten weeks during the crossover trial, a linear mixed model was performed in which the dependent variable was pain intensity (VAS). The independent variables consisted of time (week 1–10), stimulation (*effective/placebo*), and subject ID in order to account for the within covariance matrix.

A repeated measure ANOVA was conducted with stimulation condition (*baseline*, *effective*, *placebo*) as independent variable, and VAS, PCS, PVAQ, BDI-II, and mFIS as dependent variables, respectively. For these latter variables, the overall means were calculated for respectively the weeks that the stimulation was *effective* or *placebo* for each individual separately (Table 3). When appropriate, *post hoc* comparisons were carried out using Bonferroni correction for multiple comparisons.

The follow-up data were analyzed using a paired-samples *t*-test between the preoperative baseline scores and the postoperative (i.e. six months) scores for VAS, PCS, PVAQ, BDI-II, mFIS, TP, and FIQ (Table 4), respectively.

RESULTS

Crossover Trial

All 11 patients completed the ten-week trial period. Data for one week (placebo stimulation) of one patient (case 10) were excluded

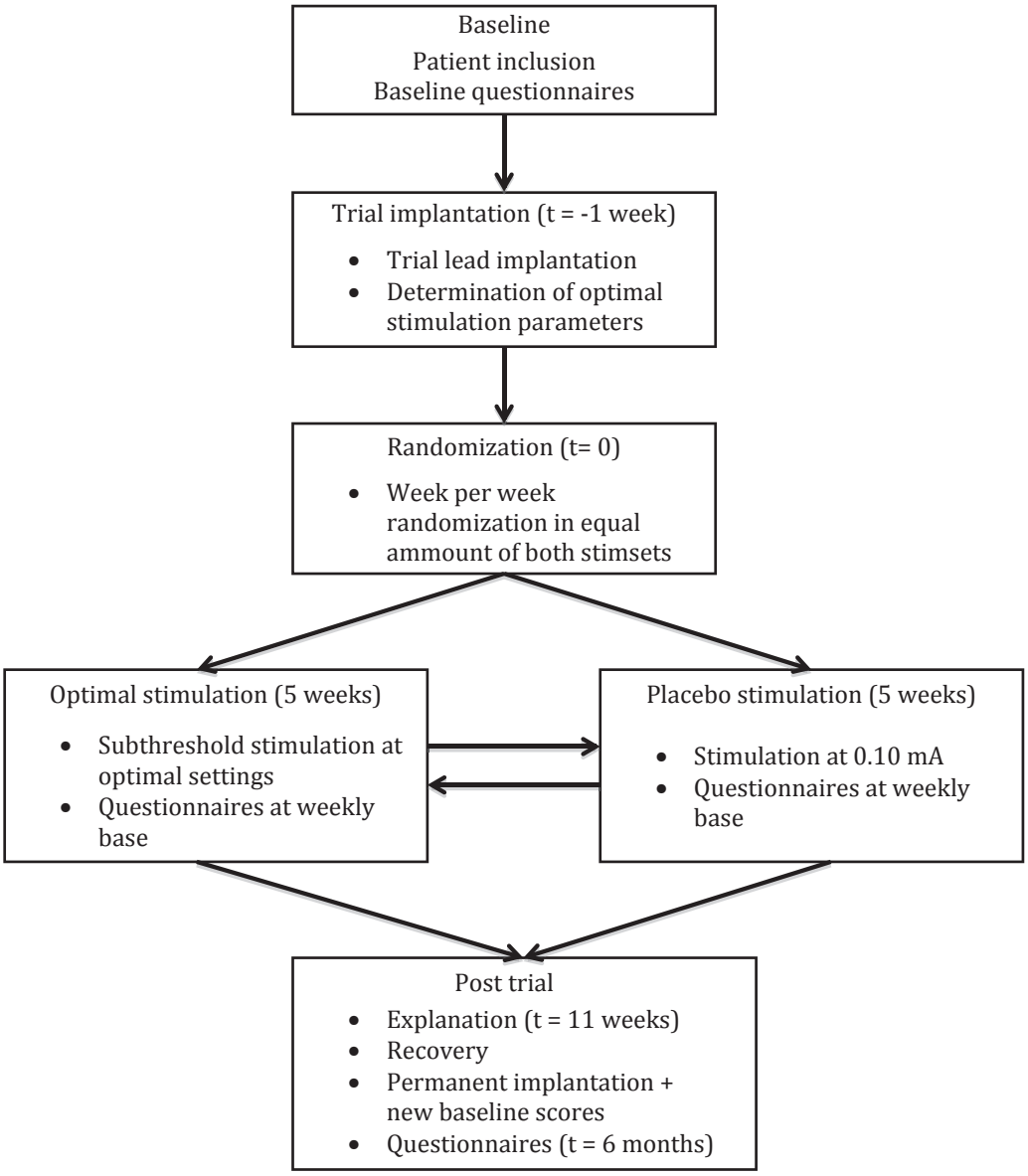

Figure 2. Flow diagram of the study.

as this patient was suffering from influenza, which may have interfered with the results.

Baseline Measurements

All acquired data of the 11 female patients, mean age of 42 years (42.45 ± 8.31 years, mean ± *SD*), were analyzed. Baseline measurements were acquired prior to surgery. The mean values were 8.64 (*SD* = 1.36; range 6–10) for pain intensity (VAS), 20.55 (*SD* = 8.83; range 1–31) for PCS, 34.00 (*SD* = 10.83; range 6–49) for PVAQ, 22.00 (*SD* = 7.35; range 6–29) for BDI-II, and 50.45 (*SD* = 15.16; range 25–75) for mFIS (Table 1; Table 3.)

Pain Intensity (VAS)

The analysis to evaluate time-related pain changes (VAS) over the ten weeks yielded no significant effect for time ($F(1,88.072) = 0.88$, $p = 0.55$) but only a significant effect for stimulation condition ($F(1,88.072) = 25.838$, $p < 0.001$). This suggests there was no significant change in pain perception due to a time effect in our design.

As for the ANOVA, the analysis showed that condition of stimulation was statistically significant ($F(2,9) = 20.84$, $p < 0.001$), suggesting that subjects perceived pain differently throughout the experiment. Specifically, when stimulation was *effective,* subjects observed less pain as compared with *baseline* and *placebo* ($p < 0.001$ and $p < 0.01$, respectively). The mean perception of pain during *effective* stimulation decreased by 39.74 and 19.79%, respectively, as compared with *baseline* and *placebo*. There also was a significant decrease of 24.87% during *placebo* stimulation compared with *baseline* ($p < 0.05$) (Figs. 3 and 4).

PCS

The analysis yielded a statistically significant effect ($F(2,9) = 5.27$, $p < 0.05$) for PCS scores. *Post hoc* comparisons showed a decrease of 35.78% of catastrophizing scores during *effective* stimulation in

Table 3. Mean (*M*) Reported Levels and Standard Deviations (*SD*) for the VAS, PCS, BDI-II, PVAQ, and mFIS at Baseline, Placebo, and Effective Stimulation.

		Baseline	Placebo	Effective
VAS	*M*	8.64	6.93	5.20
	SD	1.36	1.80	1.24
PCS	*M*	20.55	17.62	13.20
	SD	8.84	9.05	7.94
BDI-II	*M*	22.00	18.69	16.74
	SD	7.35	10.36	10.36
PVAQ	*M*	34.00	29.82	26.54
	SD	10.83	13.22	12.63
mFIS	*M*	50.45	46.49	42.13
	SD	15.16	19.30	16.89

VAS, visual analogue scale for fibromyalgia-associated pain (range 0–10); PCS, pain catastrophizing scale (range 0–52); BDI-II, Beck Depression Inventory 2nd edition (range 0–63); PVAQ, pain vigilance and awareness questionnaire (range 0–80); mFIS, modified fatigue impact scale (range 0–84).

Table 4. Mean (*M*) Reported Levels and Standard Deviations (*SD*) for the VAS, PCS, BDI-II, PVAQ, and mFIS Preoperative and Postoperative.

		Preoperative	Postoperative (6 m)
VAS	*M*	7.62	4.26
	SD	1.70	3.15
PCS	*M*	17.00	12.56
	SD	7.98	9.40
BDI-II	*M*	22.44	23.33
	SD	15.27	15.53
PVAQ	*M*	28.56	25.33
	SD	11.99	15.27
mFIS	*M*	54.33	47.11
	SD	18.59	24.24
TP	*M*	14.78	12.33
	SD	1.99	3.50
FIQ	*M*	58.80	43.06
	SD	12.80	17.17

VAS, visual analogue scale for fibromyalgia-associated pain (range 0–10); PCS, pain catastrophizing scale (range 0–52); BDI-II, Beck Depression Inventory 2nd edition (range 0–63); PVAQ, pain vigilance and awareness questionnaire (range 0–80); mFIS, modified fatigue impact scale (range 0–84); TPs, positive trigger points (range 0–18); FIQ, fibromyalgia impact questionnaire (range 0–100).

comparison to *baseline* ($p < 0.05$). Furthermore, a marginal significant effect was achieved when comparing *effective* stimulation with *placebo* ($p = 0.08$), demonstrating a decrease of 25.08% (Figs. 3 and 4).

BDI-II

The statistics for the BDI scores showed a trend to significance ($F(2,9) = 3.45$, $p < 0.08$), indicating that during stimulation, depression scores tend to be lower.

PVAQ

No statistically significant effect could be obtained for the PVAQ scores between the three conditions (*baseline*, *effective*, and *placebo*) ($F(2,9) = 2.72$, $p = 0.12$).

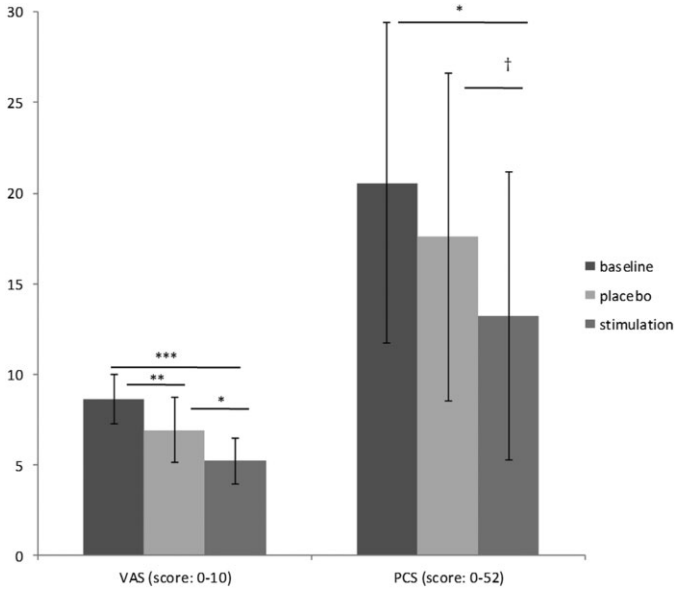

Figure 3. Mean reported levels of pain intensity on a visual analogue scale (VAS) and pain catastrophizing scores on Pain Catastrophizing Scale (PCS) at *baseline*, *placebo*, and *effective* stimulation. Asterisk indicates statistical significance (†$p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). Each column represents the mean ratings cross time and the standard deviation.

mFIS

As for mFIS, analysis revealed no significant effect for the three conditions ($F(2,9) = 2.60$, $p = 0.13$).

During the crossover trial period, no significant adverse events occurred, except local inflammation at the externalization site of the trial lead in one patient. Antibiotic treatment was sufficient to resolve this problem. The patients reported no side effects, except local headache following surgery responding to simple analgesic treatment.

Six Months Follow-Up

All 11 patients were given the opportunity of permanent implantation. Permanent implantation followed in nine patients (Cases 1, 3–5, 7–11; Table 1). Surgery was performed in December 2008; follow-up scores were obtained in June 2009. During the follow-up period of six months, no significant adverse events occurred (see Fig. 4).

Baseline Measurements

All acquired data of the nine female patients were analyzed. Baseline measurements were acquired prior to surgery. The mean values were 7.62 ($SD = 1.70$) for VAS, 17.00 ($SD = 7.98$) for PCS, 28.56 ($SD = 11.99$) for PVAQ, 22.44 ($SD = 15.27$) for BDI-II, 54.33 ($SD = 18.59$) for mFIS, 14.78 ($SD = 1.99$) for TP, and 58.80 ($SD = 12.80$) for FIQ (Table 4).

Pain Intensity (VAS)

A significant difference between baseline (7.62 ± 1.70) and six months (4.26 ± 3.15) could be found ($t(9) = 2.75$, $p < 0.05$). The mean decrease of 44.09% suggests a beneficial effect of stimulation on pain perception (Table 4).

PCS

For the catastrophizing component of pain perception, analysis yielded a significant difference between baseline (17.00 ± 7.98) and scores at six months (12.56 ± 9.40) ($t(9) = 2.18$, $p < 0.05$) (Table 4).

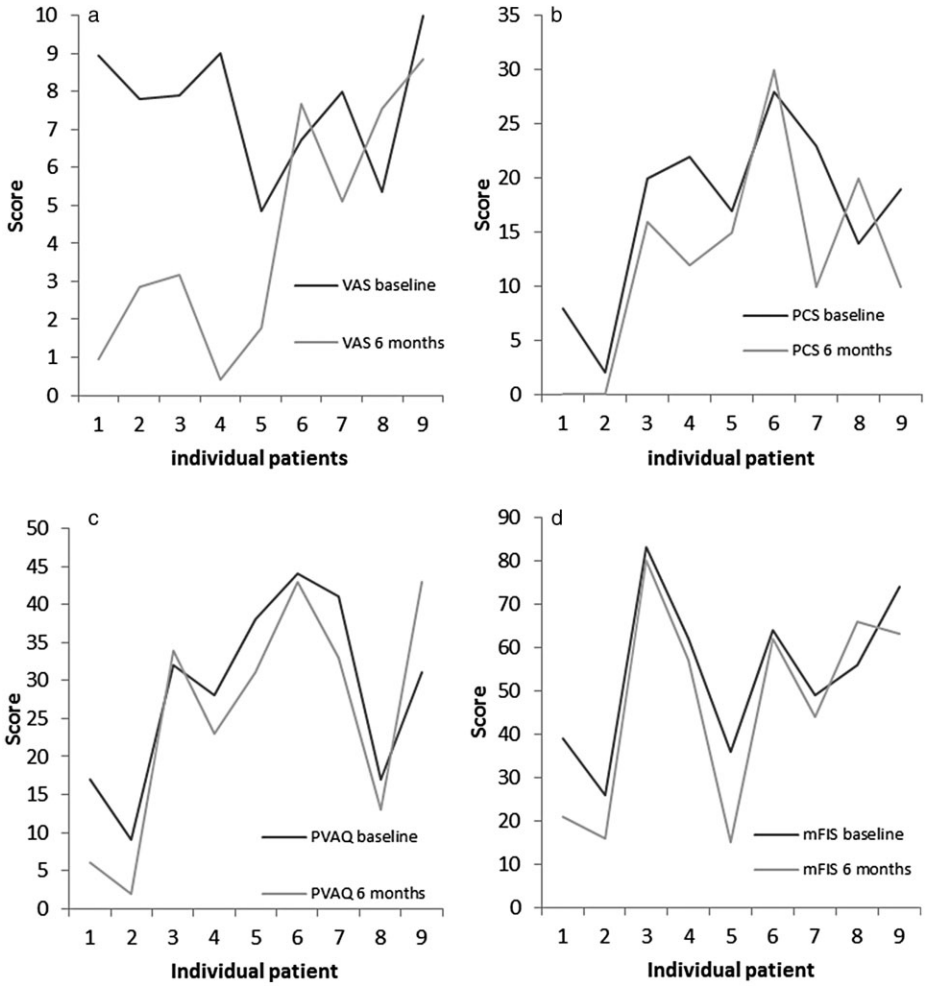

Figure 4. Individual reported scores at baseline and follow-up at six months of stimulation for a. visual analogue scale; b. pain catastrophizing scale; c. pain vigilance and awareness questionnaire; d. modified fatigue impact scale (mFIS).

BDI-II

The statistics for the BDI scores showed no significant result ($t(9) = -0.26$, $p = 0.78$) (Table 4).

PVAQ

No statistically significant effect could be obtained for the PVAQ scores ($t(9) = 1.40$, $p = 0.20$) (Table 4).

mFIS

As for the mFIS scores, analysis revealed a significant effect between baseline (54.33 ± 18.59) and scores at six months (47.11 ± 24.24) ($t(9) = 2.75$, $p < 0.05$) (Table 4).

TPs

Concerning the number of TPs, a significant difference between baseline (14.78 ± 1.99) and six months follow-up (12.33 ± 3.50) could be noticed ($t(9) = 2.93$, $p < 0.05$) (Table 4).

FIQ

Statistical analysis revealed a significant decrease comparing baseline scores (58.80 ± 12.80) with follow-up scores at six months (43.06 ± 17.17) ($t(9) = 2.51$, $p < 0.05$) (Table 4).

DISCUSSION

Our results provide evidence that 1) ONS is beneficial in the treatment of fibromyalgia in a placebo-controlled manner: VAS and PCS decreased significantly; 2) ONS exerts beneficial effects on pain (VAS, PCS, TP), fatigue (mFIS), and overall fibromyalgia-related symptoms (FIQ) six months after implantation; 3) subsensory threshold stimulation in ONS is feasible to provide placebo-controlled results.

Subsensory Threshold Stimulation

Until now, no placebo-controlled studies have been performed, both in spinal cord stimulation and in PNS. This is based on the firm belief that paresthesias are mandatory for effectiveness of stimulation based on the gate control theory postulated by Melzack and Wall. This theory suggests that pain is transmitted via unmyelinated C and A-delta fibers. Activation of the large myelinated A-beta fibers enables the inhibition of transmitting noxious input to the brain (21) and results in paresthesias (29,30). However, our data suggest that subsensory threshold stimulation is capable of suppressing pain in fibromyalgia. This suggests that placebo-controlled studies can be performed using this design.

Of the 11 patients implanted during this crossover design, two had a possible placebo response, and two did not respond to ONS.

This response rate is in accordance with ONS literature in primary headache syndromes (19,31). However, recognition of two placebo-positive patients (18%) is a new, but expected, finding in ONS. A placebo response is encountered in most available pain treatments and may get as high as 35% (23).

Fibromyalgia and ONS

In the placebo-controlled crossover trial part of this study, the results show a significant decrease in pain intensity (VAS) and PCS during *effective* stimulation. The placebo control allows for an objective evaluation of these effects.

The strength of the crossover trial part of this study is the ten-week trial period. This brings a higher risk of complications, mainly infectious, but allows to rule out the time effect of the stimulation. A noteworthy difference in pain solely caused by the ten-week time effect could not be found. This rules out the beneficial effects of weekly visits to healthcare providers and long-lasting after effects of the weeks of *effective* stimulation. Summarizing this information, beneficial effects on fibromyalgia-related pain could be ascribed to ONS with a high certainty.

As for the long-term results, ONS seems to be effective after six months of stimulation. The decreases in fibromyalgia-related VAS pain scores and the catastrophizing aspect of pain (PCS) seem to be consistent. A mean decrease of 44.09% on VAS compared with baseline ($p < 0.05$) can be noted after six months of stimulation, compared with the mean decrease on VAS of 39.74% ($p < 0.001$) during the trial phase of this study. Besides the decrease of these scores, significant decreases were found for the mFIS and FIQ. This suggests an improvement of the fibromyalgia-related symptoms after long-term stimulation. Interestingly, a significant decrease in the the number of TPs eliciting pain can be found as well. As TPs are involved in diagnosing fibromyalgia (1), this decrease might suggest a general improvement in the disease.

In comparison with the results of Thimineur et al., the decrease in pain scores during the crossover period is less impressive (20). Thimineur et al. reported a mean decrease in VAS over six months of approximately 60%. In this study, we achieve almost 40% during the crossover period. However, at six months follow-up, we find a mean decrease in VAS of almost 45%, which is still lower in comparison with Thimineur's results. The lower suppression during the crossover period may be explained by the short duration of stimulation during the trial period (weeks compared with six months of continuous stimulation). The lower decrease on VAS also might be explained by the subsensory threshold stimulation parameters during trial period and lower stimulation parameters during the follow-up period. In a recent positron emission tomography (PET) study, less effective stimulation with few paresthesias correlated with less pain suppression (32).

Another explanation might be the individual differences in response to stimulation. A look at the individual scores presurgery and after six months of stimulation shows variable reactions to stimulation. In future research, this might help to sort out groups of high responders and low responders to treatment.

Subthreshold stimulation may hypothetically still exert its effect via the gate control theory by activation of fewer A beta fibers, insufficient to generate paresthesias.

However, in pain syndromes such as migraine, the effects of stimulation are not restricted to the area of paresthesias (32). This might suggest that other mechanisms are involved in pain suppression by ONS. The connections in the trigeminocervical complex between afferents of the Nucleus Trigeminalis and the Greater Occipital Nerve (33) might explain these effects. Patients suffering from Chiari malformation and spinal stenosis might mimic or present themselves with the same symptoms as patients suffering from fibromyalgia. The pathology is located at this high cervical complex in these cases as well (34). However, central effects on cortical and subcortical regions involved in pain might be playing a role. A PET scan study by Matharu et al. shows changes in the activity of cerebral structures caused by ONS (32). Further research is needed to understand the mechanism of action and to explain the widespread effects on bodily pain as seen in this study.

CONCLUSION

Although the mechanism of action of ONS on fibromyalgia is still unclear, the data presented demonstrate a placebo-controlled beneficial effect on pain in fibromyalgia, which is confirmed after permanent implantation at six months follow-up. Besides local inflammation at the externalization site of the electrode, no serious adverse events occurred.

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Authorship Statement

Mark Plazier: patient selection, surgery, data collection, design study, preparing manuscript
Ingrid Dekelver: patient selection, data collection
Sven Vanneste: design study, preparing manuscript
Gaëtane Stassijns: patient selection, data collection
Tomas Menovsky: surgery, preparing manuscript
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COMMENTS

Despite the lack of consensus regarding underlying mechanism (or even the mere existence of the diagnosis per se) of fibromyalgia (FM), there is a tremendous need in safe, effective, reliable and consistent treatment that would alleviate pain and suffering in many thousands of affected individuals. The introduction of occipital nerve stimulation (ONS) for FM in 2007 (1) was considered an important breakthrough in FM treatment and in widening the spectrum of neuromodulation indications (2). Subsequent analysis of FM patients treated with ONS showed appearance of high frequency EEG activity (24–28 Hz) in the anterior cingulate gyrus during ONS compared to no stimulation using low-resolution brain electromagnetic tomography (LORETA) (3) indicating at least some component of central mechanism of action of peripheral neurostimulation. The study printed here adds legitimacy to the approach and provides a convincing set of data in a prospective cohort of FM patients. As a matter of fact, placebo-controlled double blind investigation fulfills the most stringent requirements for modern neurostimulation research and would be expected to satisfy regulatory authorities in granting approval for this treatment indication. The next step in this direction would be to gather longer follow up data and then duplicate results in other clinical centers worldwide. Knowing refractoriness of pain and severity of disability in some FM patients one may expect it to become an important indication for peripheral nerve stimulation in the decades to come. Therefore, the other two issues that need to be addressed would be cost-effectiveness of this treatment and its (albeit it quite minimal) invasiveness; perhaps with development of smaller, simpler and cheaper devices that are dedicated for ONS applications, these issues will be successfully solved.

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The authors present a double-blinded peripheral nerve stimulation pilot study in fibromyalgia with encouraging results. The ability for peripherally positioned suboccipital electrodes to palliate this central phenomenon suggests convergence of segmental and supraseg-mental mechanisms via the cervicotrigeminal tract. Although these mechanisms remain unclear, it is encouraging to see functional and pain improvements, giving hope for many suffering from this significant and often undertreated condition.

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This paper is a useful addition to the previous publication on ONS for fibromyalgia (FMS) by Thimineur , et al, (1). Not only is this a double-blind placebo controlled randomized trial, but the authors were able to demonstrate that using a stimulation current of 0.10 mA represented placebo stimulation as an alternative to effective sub-threshold stimulation. This was determined in a randomized double-blind manner in each patient over the 10-week trial period. Further blinding was assured by using a physician trained in physical medicine and rehabilitation who undertake the clinical evaluation without knowing what programming parameters were used and another physician from neurosurgery who undertook the programming was blinded from the clinical evaluation. A reduction in the VAS of almost 40% was achieved during the trial and this decreased further to 45% at 6 months. Also noted was a significant change in the pain catastrophizing scale (PCS) of 35.78%, which is statistically significant. The other metric that improved at 6 months was the modified fatigue impact scale (mFIS). This was also statistically significant. In summary, these results provide

sufficient evidence that in a placebo-controlled manner ONS is effective for the treatment of fibromyalgia. It is also of benefit in regard to reducing tender points, VAS and PCS. Also of relevance to future studies of neuromodulation is the fact that it is feasible to use subthreshold stimulation for determining placebo-controlled data.

While the mechanism of peripheral nerve stimulation is based on the Gate Control theory, subthreshold stimulation may also activate the Gate Control but activate fewer AB fibers, that are insufficient to generate regional paresthesia. The authors do postulate other mechanisms such as activation of the spinal tract of V by afferents traveling in the C2-C3 nerves to explain pain suppression by ONS. The recent positron emission tomography (PET) study in migraine patients by Matharu et al. (2), found significant changes in the regional cerebral blood flow (rcBF) in the dorsal rostral Pons, anterior cingulate cortex (ACC) and cuneus that were directly correlated with pain scores. In the ACC and left pulvinar rCBF correlated directly with stimulation-induced paresthesiae.

This study not only moves the science of neuromodulation ahead, but provides good evidence that a poorly understood syndrome like FMS can be more effectively managed by neurostimulation. A larger multicenter study would be useful in the future to validate these results.

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Comments not included in the Early View version of this paper.

