Original Articles

C2 Nerve Field Stimulation for the Treatment of Fibromyalgia: A Prospective, Double-blind, Randomized, Controlled Cross-over Study

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ABSTRACT

Background: Fibromyalgia is a condition characterized by widespread chronic pain. Due to the high prevalence and high costs, it has a substantial burden on society. Treatment results are diverse and only help a small subset of patients. C2 nerve field stimulation, aka occipital nerve stimulation, is helpful and a minimally invasive treatment for primary headache syndromes. Small C2 pilot studies seem to be beneficial in fibromyalgia.
Methods: Forty patients were implanted with a subcutaneous electrode in the C2 dermatoma as part of a prospective, double-blind, randomized, controlled cross-over study followed by an open label follow up period of 6 months. The patients underwent 2 week periods of different doses of stimulation consisting of minimal (.1 mA), subthreshold, and suprathreshold (for paresthesias) in a randomized order. Twenty seven patients received a permanent implant and 25 completed the 6 month open label follow up period.
Results: During the 6 week trial phase of the study, patients had an overall decrease of 36% on the fibromyalgia impact questionnaire (FIQ), a decrease of 33% fibromyalgia pain and improvement of 42% on the impact on daily life activities and quality. These results imply an overall improvement in the disease burden, maintained at 6 months follow up, as well as an improvement in life quality of 50%. Seventy six percent of patients were satisfied or very satisfied with their treatment. There seems to be a dose−response curve, with increasing amplitudes leading to better clinical outcomes.
Conclusion: Subcutaneous C2 nerve field stimulation seems to offer a safe and effective treatment option for selected medically intractable patients with fibromyalgia.

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Introduction

Fibromyalgia is pain syndrome characterized by widespread chronic pain, consisting of axial pain, left- and right-sided pain, and upper and lower segment pain lasting for at least three months [1]. Fibromyalgia symptoms are not restricted to pain, but include also non-restorative sleep, fatigue, headaches and mood disorders. Since there are no consistent findings on physical or technical examinations, the diagnosis is mainly clinical [2]. The American College of Rheumatologists (ACR) recognized fibromyalgia as a diagnostic disorder and proposed diagnostic criteria in 1990 [3] with a proposal for revision in 2010 [4] which focused on a self-report questionnaire taking into account 18 pain areas and questions concerning fatigue, memory disturbances, lower abdominal cramps, depressive mood, and headache as diagnostic criteria. The previously required tender point examination was removed from the original criteria in the proposed revision [4]. Epidemiological studies show a prevalence up to 8%, with a female to male ratio of between 7:1 and 9:1 [5]. Since the health care utilization in this patient population is high, the syndrome carries a high economic burden. The estimated direct medical costs are up to €10.087 per year per patient in France and up to $11,049 per patient per year in the United States [6,7].

The exact mechanism underlying this pathology is not known, however clinical functional imaging and neurophysiological testing suggests it is related to central sensitization with decreased inhibitory descending pain control [8]. Treatment options are as diverse as their outcomes. Both pharmacological and non-pharmacological

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Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Patients able to provide informed consent to participate in the study.	1. Patient has current evidence of any psychiatric disorder, as documented by the DSM-IV-TR criteria with psychotic characteristics (e.g. bipolar disorder, major depressive disorder).
2. Patient has had chronic widespread pain for at least 3 months in all 4 body quadrants.	2. Patient has been diagnosed with any disease mimicking the symptoms of the Fibromyalgia Syndrome (e.g. Epstein Barr, autoimmune diseases, etc.) that is not currently being treated or has not been stable for at least 6 months.
3. Patient has at least 11 out of 18 tender points based on the tender points examination.	3. Patient is currently participating in active menopause.
4. Patient has attempted "best" medical therapy and has tried and failed at least three documented medically supervised treatments (including, but not limited to drugs, physical therapy, acupuncture, etc.).	4. Patient has been diagnosed with sleep apnea and is not currently involved in a treatment regime.
5. Patient medication has remained stable for at least 4 weeks prior to baseline data collection.	5. Patient has a history of substance abuse or substance dependency in the past 6 months prior to baseline data collection.
6. Psychological screening has been completed and the patient has been cleared by a psychologist as a suitable study candidate.	6. Patient currently participating in another clinical study.
7. Patient agrees not to add or increase medication throughout the randomization trial period of the study.	7. Patient with demand-type cardiac pacemakers, an infusion pump or any implantable neurostimulator device.
8. Patient is willing to cooperate with the study requirements including compliance with the treatment regimen and completion of all office visits.	8. Patient is likely to require an MRI evaluation in the future.
	9. Patient is not willing to maintain current medication regimen.

modalities are used [2]. Physical therapy, both active and passive, and psychological treatment tends to improve symptoms [9]. Concerning the pharmacological treatment, analgesics, opioids, antidepressant drugs, and anticonvulsants have shown some usefulness [9,10]. However, a group of patients remains refractory to treatment. In various pathologies this is the point in which surgical treatments like neuromodulation find their place. One new treatment option could be neuromodulation for patients intractable to conservative medical practice [11–15]. Stimulation via a subcutaneous implant of an electrode in the area of the greater occipital nerve can be performed in a minimally invasive way which has been described by Weiner and Reed for the treatment of medically intractable headache syndromes [16]. Since its inception it has been investigated as a potential treatment for many different head and facial pain syndromes [17–19]. It delivers electrical pulses in the area supplied by the greater occipital nerves, which arise from the second cervical nerve complex, and is described as nerve field stimulation [20]. The mechanism of action is uncertain, but supposed to be due to the connections at the trigeminal–cervical complex, a connection between the greater occipital nerve and brainstem structures including the nuclei of the trigeminal nerve and autonomic nervous system [14,21]. Subcutaneous nerve field stimulation of the area supplied by the greater occipital (C2) nerve modulates brain activity in several important regions involved in pain perception as shown by functional imaging including fMRI and PET techniques [22–24].

A serendipitous finding by Thimineur is that in patients with fibromyalgia, who also had headaches, and were treated for the headaches by C2 nerve stimulation, showed that not only the headaches improved, but also the associated wide spread bodily pain and fatigue, leading to an increased quality of life [13]. This was followed up by a small pilot study in a placebo-controlled way [15], supporting the initial non-placebo-controlled study [13]. Guided by these positive results the authors performed a randomized double blinded controlled trial, with different doses in randomized order for periods of 2 weeks, and concluding with an open label follow-up. The study goals were to determine the safety and efficacy of C2 nerve stimulation in the treatment of fibromyalgia. The primary outcome parameter was a reduction in fibromyalgia related disease burden as measured by the Fibromyalgia Impact Questionnaire.

Methods

Participants

Forty patients suffering from fibromyalgia were enrolled in accordance with the eligibility criteria presented in Table 1 at the University Hospital Antwerp, Belgium. Patients were diagnosed as having fibromyalgia by a specialized physician of the department of physical health and rehabilitation. Comorbid psychiatric disorders were excluded by a specialized pain psychologist. In summary, patients had to fulfill the ACR-90 criteria which ruled out mimicking pathologies. Figure 1 shows a diagram of patient enrollment. All patients gave signed informed consent prior to enrollment. The ethical review board of the University Hospital Antwerp approved this study.

Surgical procedures

Trial implantation was performed under local anesthesia in the operating room. After shaving a small area of the occipital scalp, a vertical incision was made at 2.6 cm left of the midline just underneath the occipital protuberans. A touhy needle was introduced in the subcutaneous plane and tunneled 5.2 cm directed to the contralateral pinna of the ear. Subsequently the electrode (Octrode, St Jude Medical, Plano, TX, USA) was inserted through the touhy needle, followed by the removal of the touhy needle. The lead was then tunneled in a sharp angle (315°) to the contralateral side to exit the skin just underneath the hairline. It was fixed to the skin with a butterfly anchor with a restraining loop (see Fig. 2A). The electrode was connected with an external trial pulse generator (Multiprogram Trial System, St Jude Medical, Plano, TX, USA).

Permanent implantation in phase II of the study was performed in a similar way, but the lead was tunneled to a small subcutaneous pocket at the contralateral cervical area in order to create a similar strain relief loop. From this pocket it was tunneled to the ipsilateral intrascapular area in order to connect to an extension lead (extension 60 cm, St Jude Medical, Plano, TX, USA). Another strain relief loop was created and the extension lead was tunneled to a subcutaneous pocket at the gluteal area in order to connect the extension lead to an internal pulse generator (Eon mini, St Jude Medical, Plano, TX, USA) (see Fig. 2B).

Trial design and interventions

The study was designed as a prospective double-blind randomized controlled cross-over study followed by an open label follow up period of 6 months.

The study was divided into two phases (Phase I, II). Phase I consisted of a trial phase of 6 weeks in which the patient used an external pulse generator. Phase II consisted of an open label follow up period after permanent implantation of the neuromodulation device.
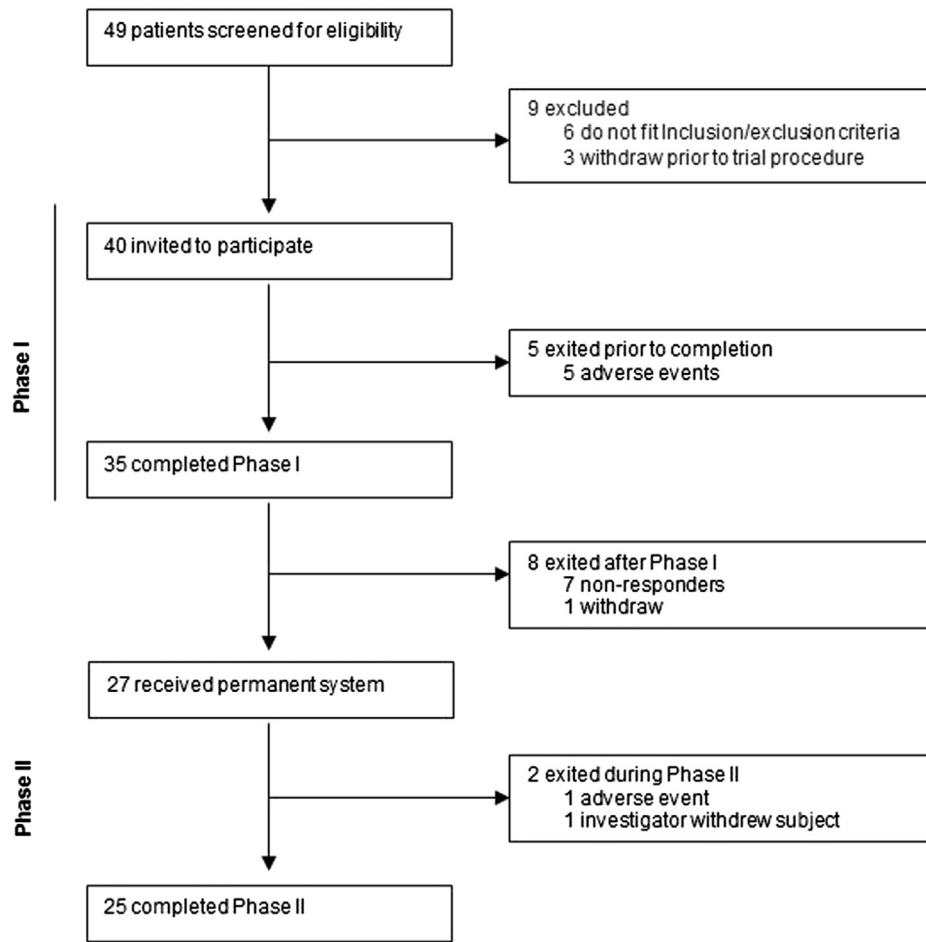
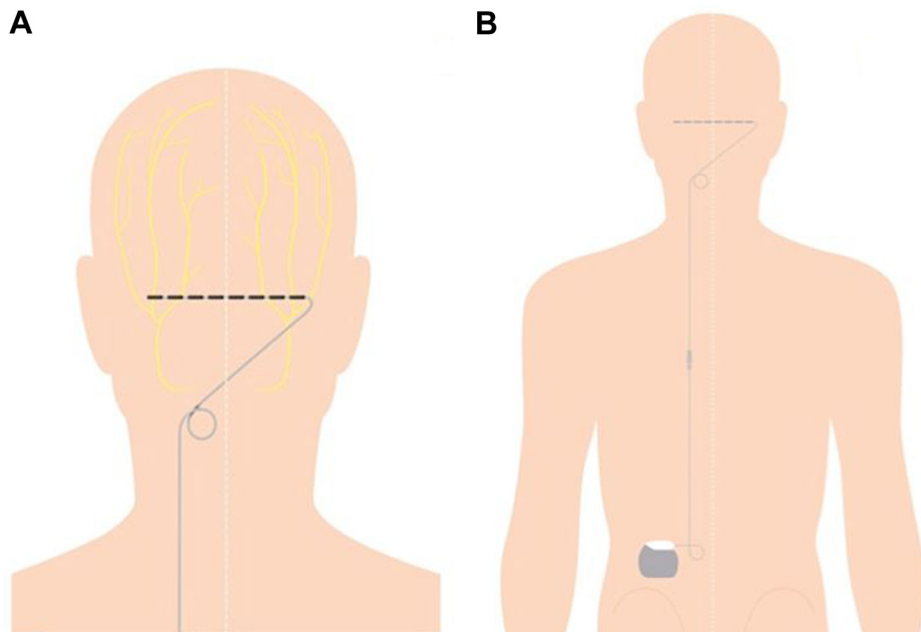**Figure 1.** Diagram participants flow.

Figure 2. Schematic overview of the C2 electrode position. A: Trial lead position and B: Permanent implantation configuration.

In Phase I (trial) patients filled out the baseline questionnaires and were implanted with the trial procedure as described above. Patients were provided with an external pulse generator (Multi-program Trial System, St Jude Medical, Plano TX, USA) with the instructions on how to use it. Patients received 5 programs to test in the first week after trial implantation (6 Hz, 10 Hz, 12 Hz, 20 Hz and 40 Hz, with a pulse width of 300 μs) [13,15]. Patients were capable of switching between the different stimulation programs and were able to 'turn on and off' the device at will, as well as adjusting the amplitude of stimulation. After that week, patients were asked to select their preferred stimulation settings, which were then used for Phase II. Patients were randomized to the study arms A and B with a cross-over after two weeks and fulfilled all three periods of two weeks of each of the different forms of stimulation:

A) "Minimal stimulation": patients were stimulated at minimal stimulation (.1 mA, the lowest possible output of the external pulse generator) for two weeks which served as a control situation. Stimulation at .1 mA is believed to be none − to minimally effective. During minimal stimulation patients received continuous stimulation of .1 mA at a pulsewidth of 300 μs over the implanted electrode.

B) "Subthreshold stimulation": patients were stimulated at sub-sensory threshold stimulation for two weeks. This threshold was determined by increasing the amplitude up till patients experienced paresthesias, and then decreasing the amplitude to 90% of this threshold, with manual pressure overlying the electrode, to ascertain no paresthesias would not be felt while lying down with pressure on the back of the head. During this form of stimulation patients did not feel stimulation, hence it could be compared to the control stimulation in condition A.

Subsequently all patients passed through to:

C) "Suprathreshold stimulation": patients were stimulated at supra-sensory threshold stimulation for two weeks. This implied that patients were aware of stimulation and they could adjust their stimulation intensity at will. Sensory threshold was determined as described in condition B and patients could stimulate up until painful sensations were experienced above this threshold. This condition serves as an open label situation.

During Phase I patients were capable to switch the pulse generator "on and off" and to adjust the amplitude of stimulation limited by the preprogrammed range (.1 mA, sub-sensory threshold or supra-sensory threshold).

For every study arm patients underwent evaluation at 2 weeks ± 2 days. If the patient responded to intervention in either arm B or C, the patient got the option of obtaining the permanent implant. A positive responder was defined as having a 20% decrease on the FIQ.

All trial leads got explanted after Phase I of the trial. Patients proceeding to Phase II had a recovery period of at least 6 weeks.

Before permanent implantation (as described above) patients filled out a new baseline. Patients were implanted with the permanent stimulation device, which was the internal pulse generator (EON mini, St Jude Medical, Plano, TX, USA). Programming parameters were unchanged compared with the chosen parameters in arm C of Phase I. Follow-up visits were scheduled at 4 weeks ± 5 days, 12 weeks ± 5 days, 18 weeks ± 5 days and 24 weeks ± 5 days in order to fill out the questionnaires and undergo physical examination.

Randomization process phase I and blinding

Patients were programmed according to the group assignment designated in the randomization envelops. Subjects and investigators were blind to the treatment groups. Programming was performed by a nurse of the department.

Outcomes

The primary outcome parameter for the efficacy of treatment is the change in Fibromyalgia Impact Questionnaire scores (FIQ). This questionnaire measures the overall impact of fibromyalgia related symptoms on the patient's life quality. The maximum score is 100, a higher score indicates a higher disease burden [25]. This questionnaire was assessed during Phase I at baseline and at the end of each of the three study arms ("minimal stimulation", "sub threshold stimulation" and "suprathreshold stimulation") as well as during Phase II at baseline and after 4-weeks, 12-weeks, 18-weeks, and 24-weeks of treatment.

The secondary outcomes are the Pain Vigilance and Awareness Questionnaire (PVAQ), Pain Catastrophizing Scale (PCS), Tender Point Examination (TPE), and Numeric Rating Scale (NRS) for pain and for quality of life. In addition we asked the overall satisfaction, quality of life, and overall symptom relief with the treatment. These assessments were acquired at the same moments as the FIQ. The Beck Depression Inventory (BDI), Modified Fatigue Impact Scale (MFIS), and the Pittsburgh Sleep Quality Index (PSQI) were assessed during Phase II after 4-weeks, 12-weeks, 18-weeks, and 24-weeks of treatment.

The PVAQ measures the preoccupation with or attention to pain, and is associated with pain-related fear and perceived pain severity. It consists of 16 items measured on a 6-point scale [26].

The PCS indicates the catastrophizing impact of pain experienced by the patient. It consists of 13 statements concerning pain experiences on a 5-point scale [27].

TPE is measured by applying a manual pressure of approximately 4 kg to the designated points in accordance with the ACR-90 [1].

The NRS was used for quality of life in which a higher score indicated a higher quality of life. NRS was also assessed for pain caused by a) fibromyalgia, b) bone pain and c) non-specific pain (like wounds or bruises), d) headache related pain. It was used to measure symptom relief and treatment satisfaction. Using an NRS we measured the quality of life, headache/migraine pain, fibromyalgia pain, the bone and joint pain, and non-specific pain. In addition, a 5-point Likert scale measured if they were overall satisfied (from −2: very unsatisfied to 2: very satisfied), measured the quality of life (from −2: greatly deteriorated to 2: greatly improved), and overall symptom relief (from 1: Poor to 5: Excellent) with the treatment. This was performed both during Phase I for the minimal, subthreshold, and suprathreshold stimulation as well as during Phase II after 4-weeks, 12-weeks, 18-weeks, and 24-weeks of treatment.

During Phase II the modified fatigue impact scale (MFIS) and the Pittsburgh Sleep Quality Index (PSQI) were acquired at baseline and after 4-weeks, 12-weeks, 18-weeks, and 24-weeks of treatment. The Beck Depression Inventory (BDI) was acquired at baseline and after 24 weeks.

The BDI provides information about depressive feelings and consists of 21 questions [28]. The MFIS is 40-item instrument designed to rate the extent to which fatigue affects perceived function [29]. The PSQI is a 19-item questionnaire which assesses sleep quality over a one month period [30].

Statistical analysis

Sample size

We calculated our sample by assuming an α level of .05 (two-sided), power of 95%, and an effect size f of .25 of the FIQ. This

resulted in a sample size of 35 for Phase I of our study. A post-calculation during the trial to detect relevant difference within the patient group in Phase II assuming an α level of .05 (two-sided), power of 80%, and an effect size f of .25 of the FIQ, resulted in a sample size of 24 patients in Phase II of our study.

We followed consolidated standards for reporting trials (CONSORT) guidelines [31,32], and used SPSS version 22.0 for all statistical analyses.

A repeated measure analysis of variance was used to compare the primary and secondary outcome measures for Phase I at baseline, and for the three study arms ("minimal stimulation", "subthreshold stimulation" and "suprathreshold stimulation"). For Phase II of the study a repeated measure analysis of variance was used to compare the primary and secondary outcome measures at baseline as well as after 4-weeks, 12-weeks, 18-weeks, and 24-weeks of treatment. A Bonferonni correction was applied to compare the individual main effects between the different stimulation designs and the baseline for Phase I, as well as for Phase II between the baseline and the different time points of measurement during the treatment. For Phase I the one-tailed Pearson correlations were obtained between the three study arms ("minimal stimulation", "subthreshold stimulation" and "suprathreshold stimulation") after subtracting the baseline scores for the different assessments.

Role of the funding source

This study was industry funded by St. Jude Medical, Plano, TX, USA. The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors approved the final report. This study is registered with ClinicalTrials.gov, number NCT00917176.

Results

A total of 49 subjects were enrolled in this study from July 2010 to August 2011 at the University Hospital Antwerp. Nine patients were excluded (18.4%). A total of 40 patients progressed to Phase I, from which 5 patients did not complete Phase I of the trial (for reasons see Fig. 1, infection $n = 1$, allergic reaction $n = 1$, lead migration $n = 3$). Of the 35 patients who completed Phase I, 7 patients (20%) were classified as non-responders and did not proceed to Phase II. One patient chose not to proceed to Phase II. A total of 27 patients proceeded to Phase II. Two patients (7.4%) did not complete Phase II (see Fig. 1, pregnancy $n = 1$, investigator's decision $n = 1$). Tables 1S and 2S show the baseline values of the study population and the diagram 2 shows the participants flow.

Safety evaluations

During the study 34 adverse events (AE) occurred in 23 subjects. 14 (41.2%) were not device or procedure-related. From the remaining 20 AEs, 14 (70%) were resolved with little to no risk for the patient. The remaining 6 (30%) resulted in additional surgery. Four serious adverse events were noted during the study, defined by needing surgical treatment and/or hospitalization. One of these events was device/procedure related where the system got infected and needed to be removed. The other serious adverse events were not device related (low back surgery, $n = 1$; umbilical scar tissue herniation, $n = 1$; severe constipation, $n = 1$).

Phase I

We noted a significant reduction on the fibromyalgia impact questionnaire for "suprathreshold stimulation" in comparison with baseline (35.89%) and "minimal stimulation" (21.87%). No significant effect was obtained between subthreshold and suprathreshold stimulation on the FIQ (see Table 2).

For the secondary outcome measures "suprathreshold stimulation" compared to baseline shows a significant decrease on the PVAQ (16.27%), the PCS (32.27%), NRS for headache (32.27%), the NRS for fibromyalgia pain (32.65%), and the NRS for bone and joint pain (33.82%). A significant improvement was obtained for the NRS quality of life (42.25%). No effect was obtained for non-specified pain between the different stimulation designs. In general, "minimal stimulation" and "subthreshold stimulation" did not differ significantly from the baseline measurements on the different secondary outcomes measures. A comparison of the different stimulation designs had no impact on patient satisfaction and NRS quality of life. See Table 2 for a general overview of the results. Significant correlations were demonstrated between minimal, subthreshold, and suprathreshold for most assessments in Phase I, indicating, the larger the response was for minimal stimulation, the larger the obtained effect was for subthreshold and suprathreshold stimulation (see Table 3).

Phase II

A follow-up of 24-weeks after the initiation of the treatments demonstrates a significant effect in comparison to the baseline on the primary outcome parameter, the FIQ (35.90%). Interestingly, at the different time points of follow-up (4-weeks, 12-weeks, 18-weeks, and 24-weeks) a significant effect was obtained compared

Table 2
Phase I: Primary and secondary outcomes at baseline and minimal, subthreshold and suprathreshold stimulation.

	Baseline	Minimal	Subthreshold	Suprathreshold	*P* value	Effect size
Primary outcome measure						
FIQ	65.66[a]	53.87[b]	51.21[b,c]	42.09[c]	<.001	.59
Secondary outcome measures						
PVAQ	41.97[a]	38.54[a]	37.34[a,b]	35.14[b]	.004	.33
PCS	23.37[a]	17.66[b]	17.14[b,c]	14.66[c]	<.001	.60
NRS						
Overall quality of life	4.00[a]	4.00[a]	4.40[a]	5.69[b]	.001	.41
Overall headache/migraine pain	6.29[a]	4.09[b]	4.60[b]	4.26[b]	<.001	.51
Overall fibromyalgia pain	6.83[a]	5.80[a,b]	5.54[a,b]	4.60[b]	.006	.32
Overall bone and joint pain	6.86[a]	5.94[a]	5.37[a,b]	4.54[b]	<.001	.39
Overall non-specified pain	4.71	4.66	3.80	3.57	.048	.22
TPE[a]	17.03[a]	14.41[b]	14.47[b]	15.97[a,b]	.011	.30
Overall symptom relief	–	2.54[a]	2.77[a,b]	3.20[b]	.015	.23
Satisfaction	–	1.17	.86	.60	.070	.15
Quality of life	–	.74	.71	.74	.987	.001

[a] Data point of one subject is missing; different superscripts indicate a significant differences (A Bonferonni correction was applied to compare the individual main effects).

Table 3
Phase I: Dose response effects for the primary and secondary outcomes at minimal, subthreshold and suprathreshold stimulation in comparison to the baseline.

	Minimal–subthreshold	Minimal–suprathreshold	Subthreshold–suprathreshold
Primary outcome measure			
FIQ	.17	.53**	.38**
Secondary outcome measures			
PVAQ	.44**	.70**	.54**
PCS	.58***	.66***	.54**
NRS			
Overall quality of life	.27	.60***	.44*
Overall headache/migraine pain	.35*	.60**	.50**
Overall fibromyalgia pain	.34*	.22	.56**
Overall bone and joint pain	.15	.13	.41*
Overall non-specified pain	.66***	.38*	.59**
TPE[a]	.36*	.13	.10

*$P < .05$; **$P < .01$; ***$P < .001$.
[a] Data point of one subject is missing.

to baseline. No significant effect was shown between the different time points of follow-up (see Table 4).

For Phase 2, we did note a significant reduction for the PVAQ (23.31), the PCS (51.20%), the NRS headache scale (36.99%), the NRS fibromyalgia pain scale (36.42%), the NRS bone and joint pain scale (36.11%), the NRS non-specific pain scale (30.40%), the BDI (36.77%), and the PSQI (24.02%) when comparing baseline with 24-weeks of follow after the initiation of treatment. In addition, the NRS quality of life improved with 50.57%; 10 of 24 patients were very satisfied (40%), 9 were satisfied (36%), 4 were neither satisfied or unsatisfied (16.0%), and 1 patient was unsatisfied (4.0%) with the treatment. A comparison between the different time points of follow-up revealed no significant effect. An overview of the results can be found in Table 4.

Discussion

Our results provide evidence that greater occipital nerve stimulation is a safe treatment for patients suffering from fibromyalgia analogous to what has been shown for the application for primary headache syndromes [17]. In this study, there was only one serious adverse event related to the procedure, which required the removal of the device because of infection. Removal of the electrode resulted in complete resolution of the problem. Furthermore the outcome data demonstrates that occipital nerve field stimulation can have a role in the management of medically intractable fibromyalgia. The overall beneficial effects on the fibromyalgia related burden decreased by 35.9% after 24 weeks. The secondary outcome measures confirm this and reveal additional beneficial effects on the quality of life, mood, fatigue, and sleep quality. These later results further strengthen the findings that the effect is robust and long-lasting.

Neuromodulation therapy for fibromyalgia has thus far been preliminary. Thimineur and De Ridder implanted patients with an occipital nerve stimulation device, with an open label follow up of 6 months and showed a beneficial effect on pain levels, mood, and fatigue [13]. However, the primary indication for implantation was intractable headaches in patients with fibromyalgia as a comorbidity [13]. The preliminary promising results lead to a second randomized controlled study with a weekly cross-over in the trial phase between active and presumed non-active (i.e. .10 mA) stimulation during 10 weeks, followed by an open label follow up period in small population of 11 fibromyalgia patients [15]. A significant effect for effective stimulation compared to non-active stimulation, and to the baseline could be obtained during the trial stimulation for pain. During the six months follow up period, scores improved for pain, pain catastrophizing, and fibromyalgia impact questionnaires. The findings of this third study corroborate with these initial studies. In Phase I we obtained an effect on both the primary and secondary outcome measure, indicating that both the pain, the attention to the pain, and the catastrophizing of the pain decreased significantly and the overall symptomatic burden improved. More importantly, these effects were obtained during both minimal stimulation, subthreshold stimulation, and suprathreshold stimulation. The most pronounced effect was demonstrated during suprathreshold stimulation. But also during minimal and subthreshold stimulation substantial effects were obtained in comparison to baseline. However, during minimal stimulation the effect was less prominent. In contrast to the previous study by Plazier and colleagues [15] the presumed inactive, i.e. sham effect of minimal stimulation seems to be effective, albeit less pronounced than higher amplitudes, since we could not obtain a significant difference between "minimal stimulation" and "subthreshold stimulation". This might be explained by the different study design, in which a longer period of sham

Table 4
Phase II: Primary and secondary outcomes at baseline and 4-weeks, 12-weeks, 18-weeks, and 24-weeks after baseline.

Primary outcome measure	Baseline	4-weeks	12-weeks	18-weeks	24-weeks	P value	Effect size
FIQ	65.54[a]	40.35[b]	39.80[b]	43.74[b]	43.50[b]	<.001	.75
Secondary outcome measures							
PVAQ	41.36[a]	36.72[b]	31.48[b]	31.76[b]	31.72[b]	.002	.55
PCS	21.24[a]	11.32[b]	10.96[b]	11.52[b]	10.80[b]	<.001	.67
NRS							
Overall quality of life	3.48[a]	6.04[b]	6.40[b]	5.96[b]	5.24[b]	<.001	.75
Overall headache/migraine pain	5.84[a]	4.96[a,b]	3.48[b]	4.08[a,b]	3.68[b]	.035	.38
Overall fibromyalgia pain	6.92[a]	4.84[b]	4.00[b]	5.00[b]	4.40[b]	<.001	.58
Overall bone and Joint Pain	7.20[a]	4.80[b]	4.36[b]	5.04[b]	4.60[b]	<.001	.62
Overall non-specified pain	5.40[a]	4.00[a,b]	3.48[b]	3.24[b]	3.96[b]	.012	.44
TPE[a]	16.40[a]	12.10[b]	12.20[b]	12.15[b]	11.55[b]	.015	.52
MFIS	55.92[a]	42.60[b]	39.10[b]	43.16[b]	38.92[b]	<.001	.69
BDI	18.60[a]	–	–	–	11.76[b]	.002	.34
PSQI	13.32[a]	10.24[b]	9.56[b]	9.88[b]	10.12[b]	<.001	.55
Overall symptom relief[b]	–	54.37	56.96	53.96	49.21	.694	.07
Satisfaction[b]	–	.50	.92	.42	.71	.187	.20
Quality of life[b]	–	.88	1.08	.92	.71	.646	.07

[a] $N = 20$, some data points are missing.
[b] Data point of one subject is missing at 24-weeks; different superscripts indicate a significant differences (A Bonferonni correction was applied to compare the individual main effects).

stimulation versus subthreshold stimulation was performed in this study compared to the previous study where patients were stimulated 5 weeks in 'minimal stimulation' and 5 weeks in 'subthreshold stimulation' in a randomized order. Another explanation might be the effectiveness of stimulation at .10 mA. Time effects of stimulation duration might build up a measurable effect. If we look at the dose–response for the three conditions we can see a clear trend in effectiveness and amplitude as well as correlation between the effects generated for each patient over the three stimulation designs. Minimal stimulation (i.e. .10 mA) might thus still exert a clinical effect [22] and the effects of minimal stimulation might become more pronounced in time analogous to what has been seen in primary headache syndromes [33]. Therefore, an output of .10 mA was not thought to be effective when it likely is. In a study by Matharu et al., non-effective stimulation resulted in less effective clinical results, but still yielded effects [22]. This fits with our findings, and suggests there is a dose–response curve with higher amplitudes yielding better clinical effects.

The follow-up of the patients further indicates that the pain suppression that is obtained after 24 weeks is similar to the effect obtained within 4 weeks of stimulation.

The exact mechanism of action of occipital nerve field stimulation is still unknown. We could hypothesize that occipital nerve stimulation exerts an effect on a variety of structures in the brain. Functional imaging studies using fMRI in a healthy individual [23], as well as PET scans in patients suffering from migraine [22,24] demonstrate brain changes associated to the stimulation. PET data demonstrate that activity in the anterior cingulate gyrus, the cuneus, and frontal cortex are modulated, structures which are involved in attention to pain, pain perception, and emotional interpretation [34]. The functional Magnetic Resonance Imaging study of Kovacs et al. [23] furthermore showed a frequency and stimulation design specific deactivation of the primary somato-sensory cortex and activation of the limbic structures [23].

Central sensitization of pain and hypervigilance to pain is hypothesized to be one of the mechanisms in developing fibromyalgia [8]. A hypervigilant state to pain is based on changes in pain thresholds, attentional reactions to pain, and emotional reactions to pain [35]. As the results of functional imaging studies suggest that greater occipital nerve stimulation exerts an effect on a central level in pain processing (pain perception and the attentional, emotional and salience related structures) this could explain why it affects fibromyalgia.

The results of the various questionnaires support this hypothesis, since pain catastrophizing behavior, vigilance and awareness to pain decreased during stimulation. This could also explain the positive evolution in time caused by treatment, since the effects do not seem to directly alter pain perception, but rather alter the pain interpretation and hyperreactivity to pain.

In conclusion, occipital nerve field stimulation exerts a beneficial and lasting effect on fibromyalgia via an unknown mechanism. It could be considered as a treatment modality in medically intractable patients. Further studies with a true placebo control are warranted as well as functional imaging studies that try to unravel the working mechanism of this promising and novel treatment approach for this enigmatic syndrome.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2015.03.002.

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