Treatment of intractable chronic cluster headache by occipital nerve stimulation: a cohort of 51 patients

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ABSTRACT

Chronic cluster headache is a rare, highly disabling primary headache condition. When medically intractable, occipital nerve stimulation can offer effective treatment. Open-label series have provided data on small cohorts only. We analyzed 51 subjects to evaluate the long-term outcomes of highly intractable chronic cluster headache with occipital nerve stimulation. Patients with intractable chronic cluster headache were implanted with occipital nerve stimulators during the period 2007-2014. Primary endpoint was improvement in daily attack frequency. Secondary endpoints included attack severity, attack duration, quality of life measures, headache disability scores and adverse events. We studied 51 patients (35 male): mean age at implant 47.78 years (range 31-70) and mean follow-up 39.17 months (range 2-81 months). Nineteen patients had other chronic headache types in addition in chronic cluster headache. At final follow-up, there was a 46.1% improvement in attack frequency ($p<0001$) across all patients, 49.5% ($p<0.001$) in those with cluster headache alone and 40.3% ($p=0.036$) in those with multiple phenotypes. There were no significant differences in response of those with or without multiple headache types. The overall response rate (defined as at least a 50% improvement in attack frequency) was 52.9%. Significant reductions were also seen in attack duration and severity. Improvements were noted in headache disability scores and quality of life measures. Triptan use of responders dropped by 62.56% resulting in significant cost savings. Adverse event rates were highly favorable. Occipital nerve stimulation appears to be a safe and efficacious treatment for highly intractable chronic cluster headache even after a mean of over three-years follow-up.

INTRODUCTION

Cluster headache is a primary headache disorder characterized by bouts during which patients experience multiple attacks of severe unilateral pain associated with cranial autonomic features [7]. When attacks occur for over one year with remissions lasting less than one month then the condition is said to be chronic. Cluster headache has a prevalence of around 0.1% [20] with 10-15% of this group suffering chronic cluster headaches (CCH) [8].

Cluster headache can be successfully treated with a range of oral and injectable medications. However, a proportion of CCH patients are intractable to all available medications. Although a unifying definition of refractory CCH is still awaited, guidelines from Goadsby *et al.* suggest that patients meet diagnostic criteria for CCH and have failed at least four classes of drugs from verapamil, lithium, methysergide melatonin, topiramate or gabapentin, with at least two from the first three agents [6]. More recently, the European Headache Federation defined refractory CCH as patients meeting ICHD-3beta criteria who continue to suffer from at least three severe attacks a week despite adequate trials of at least three of the following: verapamil, lithium, oral or IV steroids, greater occipital nerve blockade, topiramate, methysergide, ergots, civamide or long-acting triptans [16]. Due to the highly disabling nature of intractable CCH, destructive surgical approaches to treatment have been investigated with disappointing results. Neurostimulation techniques involving peripheral and central targets have now emerged as promising therapies. Peripheral stimulation of the occipital nerve has been investigated as a potentially useful treatment for chronic migraine (CM) in a limited number of randomized control studies [11; 21; 24] and for CCH in a number of small open label series [1; 2; 4; 5; 12; 14; 19; 22].

We report the long-term follow-up of 51 intractable CCH patients treated with occipital nerve stimulation (ONS).

METHODS

Patients

Patients with intractable CCH seen in the headache clinic at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK were offered ONS. Patients were reviewed and operated on by a single multidisciplinary headache team, consisting of headache specialists, neurosurgeons and headache specialist nurses with access to psychology and psychiatry services. Implants took place over a period from October 2007 to June 2014. Follow-up visits occurred every three months for the first year and then every six to twelve months thereafter. All patients fulfilled the International Classification of Headache Disorders (ICHD) 2nd edition and revised ICHD-3beta diagnostic criteria for CCH as well as also the proposed criteria for intractable CCH [6; 8]. Under the supervision of our institution's Clinical Effectiveness Supervisory Committee with arrangements for clinical governance, consent and audit, we offered ONS to patients with intractable CCH. The procedure was provided on the basis of a "humanitarian intervention". In addition, ethics board approval for data collection and publication was granted by Northwick Park Hospital Research Ethics Committee, Hampstead, London, UK.

Surgical Procedure

ONS systems were implanted as described elsewhere [9]. Bilateral octad electrodes were placed in all patients (Table 1). Medtronic systems were implanted in 48 (94.1%) and St Jude Medical systems in 3 (5.9%). Patients did not undergo trial stimulation. Implantable pulse generators (IPG) were placed in subclavicular or abdominal pockets dependent on patient preference.

At initial programming, frequency was set at 60Hz with a pulse width of 240μs. Polarity of the electrodes was adjusted during follow up visits to ensure comfortable bilateral paranesthesia in the occipital region. Patients used continuous stimulation but were able to adjust the amplitude. Medications were changed at the discretion of the headache specialist.

Data Collection

Data were collected prospectively and entered onto a clinical database (Microsoft Excel, Microsoft Corporation, Redmond, WA, USA). Data including demographics, diagnosis, attack frequency, previous and current treatments, and adverse events were recorded. Patients prospectively completed headache diaries recording the frequency, severity on a verbal rating scale (VRS; 0=no pain to 10=extreme pain) and duration of cluster headache attacks for one month prior to implant and two weeks prior to each follow-up visit. Diaries were used to calculate mean daily attack frequency, severity and duration over these periods of time. Where multiple headache types were present, patients completed separate diaries for each.

Migraine Disability Assessment Scores (MIDAS) and Headache Impact Test 6 Scores (HIT-6) were recorded pre- and post-ONS to monitor headache related disability. Although MIDAS has not been validated for its use in CCH, it has been used extensively in the assessment of other primary headache disorders including cluster headache [22]. Euro-QoL, Short Form 36 Questionnaires (SF36), Beck Depression Inventory II (BDI-II), Hospital Anxiety (HAD-A) and Hospital Depression (HAD-D) Scores were used to monitor quality of life and mental state.

Primary outcome measure was improvement in mean daily attack frequency at final follow-up compared to baseline. Response was defined as a 50% or more reduction in mean daily

attack frequency. Secondary outcome measures included attack severity, attack duration, headache-related disability scores, affective measures and quality of life scores.

Statistics

All statistical analyses were conducted using IBM SPSS Statistics version 22 (IBM Corp. Int.). A last observation carried forward technique was used in the case of missing data. Descriptive statistics were summarized as appropriate. Data is presented as mean ±SD, range and frequencies. Paired and independent t-tests were used to compare treatment effect as appropriate. All statistical tests were two-sided with a significance level of 95%.

RESULTS

Patient demographics

Thirty-five men and 16 women with a mean age of 47.78 years (range 31-70 years) were implanted. Mean duration of chronic cluster headache at implantation was 7.88 years (range 2-43 years). The mean number of medications prior to implant was 12.57 ±2.91 (range 7-21). (Supplementary Table 1). Nineteen patients (37.3%) had other chronic headaches in addition to CCH: 13 had CCH and CM, three had CCH and short-lasting unilateral neuralgiform headache attacks (SUNHA) and three CCH, CM and SUNHA. All kept separate diaries for each phenotype throughout follow-up. Table 2 provides demographic data for the cohort.

Whole Cohort

Mean follow-up time was 39.17 months (range 2-81). At follow-up four patients had had their implants removed, 3 for lack of efficacy and one for intractable neck pain secondary to lead tethering. Figure 1a shows the percentage improvement in daily attack frequency over

the follow-up period. At final follow-up, 52.9% (n=27) of patients achieved at least a 50% reduction in daily attack frequency (i.e. were classed as responders). Mean daily attack frequency fell by 46.1% (±43.7) ($p<0.001$). Over the course of follow-up, 47.1 % (n=24) patients reported over six months of continuous pain-freedom. The mean duration of pain freedom was 16.25 months (range 6-48). Significant reductions were also seen in attack intensity (26.4%) and duration (43.3%) (Table 3). Across the cohort, significant improvements were observed in MIDAS (-34.92), HIT-6 (-7.05), HAD-A (-2.04), HAD-D (-2.82) and BDI-II (-4.77) scales. Quality of life scores showed improvements but only that in SF-36 mental composite score was significant (Table 4). Non-responders to ONS failed to show any improvement in any headache disability, affect or quality of life scores. Responders showed significant improvements in all headache disability scores and affective scores as well as SF-36 mental composite score (Supplementary Table 2). Patient estimate of overall CCH improvement was 53.7% (±38.60). Differences in outcomes of responders and non-responders are shown in Supplementary Table 3.

Chronic cluster headache alone

In the 32 patients with CCH alone, mean follow-up time was 42.59 months (range 2-81). Figure 1b shows the change in daily attack frequency over follow-up. A 50% response was observed in 53.1% (n=17) patients. Mean daily attack frequency reduced by 49.5% (±43.84) ($p<0.001$). Significant improvements were also seen in daily attack severity (25.0%) and duration (43.2%) (Table 3). Significant change was seen in MIDAS (-47.66), HIT-6 (-7.62), HAD-A (-2.03), HAD-D (-2.81) and BDI-II (-6.43). However, no significant improvements were observed in any quality of life measures (Table 4).

Multiple phenotypes including CCH

In the 19 patients with multiple headache phenotypes, the mean follow-up time was 33.42 months (range 13-76). The 50% response rate at final follow-up was 52.6% (n=10) which was not significantly different to that of CCH alone (p=0.973). Change in daily attack frequency over follow-up is shown in figure 1b. No difference was seen in change in daily attack frequency between the groups at any time-point. Significant improvements were also seen in attack intensity (28.8%) and duration (43.5%) (Table 3).

In responders, 4/8 CM showed improvement (defined as a more than 30% improvement in moderate-to-severe headache days) and 3/4 SUNHA also showed improvement (defined as a 50% or more reduction in daily attack frequency). In non-responders, 5/8 CM improved with ONS.

Those with multiple phenotypes showed significant improvements in HIT-6 (-6.10) and EQ-VAS (10.38) scales but in no other disability, affect or quality of life measurement (Table 4).

Triptan use

With regards to triptans, 9 patients stopped and 13 were able to decrease their use by more than 50%. Monthly triptan use was 36.82 ±32.7 (range 0-112) prior to and 19.51 ±33.07 (range 0-120) post ONS ($p<0.001$). The average cost in the UK for injectable Sumatriptan is currently £20.50 a dose translating to a saving of £407.19 ±514.98 (range 0-£1722) per-patient per-month. Responders averaged a monthly reduction of 29.37 ±25.76 doses ($p<0.001$) resulting in a saving of £604.37 ±519.52 per-patient per-month (Supplementary Table 3c).

Preventative medication use

Twenty-seven patients were taking preventative medications at baseline. Four patients were able to stop all preventative medications and in total 17 patients made reductions to their drugs.

Time to effect and recurrence of attacks

Time to first reported 50% improvement in cluster headache attacks was recorded in 37 patients with a mean of 6.86 months ±7.33 (range 1-42). Time to reach maximum reported improvement was 21.69 months ±15.06 (range 2-54). Eighteen patients had their ONS switched off at some point (13 due to battery depletion, five due to lack of efficacy and one due to explantation). The mean time of ONS switch-off in these subjects was 7.29 months (range 2-18). In 12 of these patients (66.7%), CCH worsened within a mean of 6.57 weeks of switch off (range 1-12).

Stimulation settings

A range of settings was employed in order to achieve the widest area of occipital paranesthesia possible. The range of amplitudes for Medtronic devices was 0.3-5.0V (mean 2.4V, median 1.5V), pulse width 309-594µsec (mean 418µsec) and frequency 58-137Hz (mean 69.5Hz). For St Jude devices; amplitude range was 0.5-2.7mA (mean 2.5mA, median 1.7mA), frequency 70-177Hz (mean 96Hz) and pulse width 309-450 µsec (mean 415 µsec).

Adverse events

A total of 81 events were recorded affecting a total of 35 patients (Table 5). The most common event was the need for battery replacement in 19 patients (37.3%), however, only 6 of these were deemed unexpected battery failure of under a year. Thirty-eight events required surgical intervention, although accounting for "expected" battery depletion this fell to 19. One patient (2.0%) suffered lead migration and two (3.9%) from erosion of electrodes through the skin. One infection was reported (2.0%) requiring medical intervention only.

DISCUSSION AND CONCLUSIONS

This is the largest series with prolonged follow-up period for ONS in CCH. In line with previous series (Table 5) we report that ONS appears to have a positive and sustained effect on otherwise refractory patients [1; 2; 4; 5; 12; 14; 17]. The most recent publications of long term follow up from Magis *et al.* and Leone *et al*. have both been on long-term follow up of ONS CCH patients [10; 13]. Magis *et al*. had a mean of 5.7 years follow up in 10 patients and reported a 70% reduction in attack frequency but no change in preventative drug use. Leone *et al.* described a responder rate of 66.7% in 30 patients with a median follow-up of 6.1 years with 10% of patients reducing preventative medications. In our group of 51 highly complex patients after mean follow-up of 39.17 months there was a significant improvement in mean attack frequency with 24 patients remaining pain free for prolonged periods of time over follow-up. Overall 52.9% of all patients exhibited response to ONS at final follow-up. There are a number of reasons why our response rate appears lower than previous series. Firstly, our series had a complex cohort of patients. From available data our patients had a longer duration of chronic disease, had failed more medications and over 1/3 had co-existing headache disorders whereas previous series had CCH alone. Our data suggests that there is no difference in outcomes of those with or without multiple headache types, a finding that is in opposition to general clinical belief. However, this needs to be clarified in larger cohorts of complex patients. Other factors include possible reporting bias in small series, for example the exclusion of patients whose devices were explanted, and the use of a trial stimulation period that we did not employ. Although no evidence exists for trial stimulation reliably selecting responders, removing those who do not respond may subject remaining patients to positive selection bias.

Headache disability scales, affect and quality of life scales did show improvement with ONS but those in the quality of life measures were not significant in the whole cohort. However, subgroup analysis of responder vs. non-responders showed a lack of improvement in any field in the non-responder cohort (Supplementary Table 2). The failure to observe significant change across all quality of life measures despite improvements in attack frequency does not indicate lack of efficacy. Similar observations have been made previously in ONS for chronic migraine [3] and is thought to reflect a "burden of normality" wherein patients have difficulty adjusting to the change in their new improved health status. Previous authors have also suggested that a lack of prolonged functional outcome is seen in the long-term following ONS for CM, speculation this is due to the loss of an initial "honeymoon period" in patients[3]. Issues regarding the suitability of the scales in measuring headache populations have also been raised [25]. Specific to our cohort, given that 37.3% had multiple phenotypes that did not all necessarily respond to ONS a significant proportion of patients would still exhibit a burden from these headaches, even if CCH had significantly improved. This is supported by a difference in disability scores in those with multiple phenotypes vs. CCH alone (Table 4).

As in previous series [2; 5; 14; 15], subjects reported a delay of several months before achieving a response (6.86 months) and suffered relapses within weeks of stopping stimulation. These observations suggest that there is a slow but reversible neuroplastic response to successful ONS.

The cost and adverse event profile of ONS for headache treatment have been a cause for controversy in the past. A recent paper estimated the mean treatment costs of ONS to be around £20,500 per case in a two year period [17]. Although the treatment cost is high, the direct cost from patients on society is significant. In our series, cost per patient in the UK from triptans alone was over £9000 per year (based on mean triptan use per patient of 37

doses a month at cost of £20.50 per dose). Following ONS, we estimate that patients reduced this expense by £4886 per annum with responders saving an average of £7252 per year. Non-responders showed a smaller saving (£2224 per annum). This non-significant reduction reflects patients in this group having derived some benefit from the procedure even if they did not reach the dictated 50% improvement in attack frequency. Shorter or less painful attacks mean patients avoided using triptans or oxygen. This saving combined with a third of patients reducing preventative drugs and the significant improvements in quality of life measures all provide a positive balance to the initial cost of treatment. Using above figures for cost of implant and changes in triptan doses, we estimate that the time to cost-effectiveness from reduction in triptan use alone is 3 years in responders (4 years in the whole group and 9 years in non-responders)

Adverse events in our series were much lower than those described in previous cohorts. In small series lead migration rates vary from 7- 50% [2; 5; 14; 22], lead fracture rates from 10-15% [2; 14; 19] and infection 10-20% [2; 14; 19]. Corresponding rates in our series were 2%, 0% and 2% respectively. The primary need for repeated surgery post-implant was to replace the battery (37.3%), however, the use of rechargeable batteries in recent years should lead to a decrease in surgical interventions and this is something we intend to explore in future publications. Our implants were all conducted by a single highly skilled surgical team. A small number of experienced surgeons conducting larger numbers of procedures have been related to lower adverse event rates [23] and our data supports this.

Weaknesses of the study include the lack of a placebo. This has been a major problem in ONS research, as it is believed paresthesia is a requirement of response. However, it is most unlikely that our observations are explained by placebo alone. The previous intractability, stable time to response across cohorts, sustained response after prolonged follow-up and relapse with ONS failure all argue against a pure placebo response. The placebo controlled

trials of ONS in migraine suggest a low placebo rate (6% [21], 17.3% [24] and 20% [11]) and there is no reason to expect different rates in cluster headache [18].

Strengths of the study include the large sample, prolonged follow-up, the prospective data collection and the "real life" nature of the data. All subjects were patients in a single specialist center implanted due to clinical need in a healthcare system where ONS was only available as a last-line treatment. The group is different from some previous cohorts in its complex nature and highly intractable nature. A reduction in attack frequency of nearly 50% in such a highly intractable group, having suffered chronic cluster headache for a mean of 7.88 years and having failed an average of 12.57 prior treatments, is a remarkable achievement.

Our group has recently published the outcomes of a similar complex patient group of 21 patients with CCH undergoing ventral tegmental area deep brain stimulation, 29% of which had failed ONS. A reduction in daily attack frequency of 60% was recorded with a 50% or more reduction in attack frequency achieved in 52%. Given the similar response rate and the more invasive nature of deep brain stimulation, it is clear that ONS should be considered first in CCH.

In conclusion, ONS can provide a marked and sustained benefit in highly intractable chronic cluster headache control even after a mean follow up of 3 years. Adverse event rates are low when implants are conducted in highly specialist centers. The initial cost of implantation may be offset by the reduced need for acute medications and improved quality of life.

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	N=51
ONS Manufacturer	
Medtronic	48 (94.1%)
St Jude Medical	3 (5.9%)
IPG	
Standard	8 (15.7%)
Rechargeable	27 (52.9%)
Standard changed to rechargeable	16 (31.4%)
Electrodes	
Octad	51 (100%)

IPG, implantable pulse generator; ONS, occipital nerve stimulator

Table 1: Information on the occipital nerve stimulator systems implanted

Age	47.78 years (±9.73) Range 31-70
Sex	
Male	35 (68.6%)
Female	16 (31.4%)
Attack Side	
Right	32 (62.7%)
Left	15 (29.4%)
Both	4 (7.8%)
Laterality	
Strictly unilateral	41 (80.4%)
Unilateral but side variable	7 (13.7%)
Bilateral	3 (5.9%)
Pattern	
Episodic transformed to chronic	30 (58%)
Chronic from onset	21 (42%)
Duration from onset of Cluster Headache	14.63 years (±11.0) Range 2-48
Duration from onset of Chronic phase	7.88 years (±6.44) Range 2-43
Co-existent headache phenotypes	19 (37.3%)
Number of headache phenotypes	
1	32 (62.7%)
2	16 (31.4%)
3	3 (5.9%)
Co-existent phenotypes	
CCH +CM	13 (25.5%)
CCH+SUNCT/SUNA	3 (5.9%)
CCH+CM+SUNCT/SUNA	3 (5.9%)
Mean number preventatives prior to ONS	12.57 (±2.91) Range 7-21
Response to GON block prior to ONS	21(41.2%)
Follow up since implant	39.17 months (±19.04) Range 2-81

CCH, chronic cluster headache; CM, chronic migraine; GON, Greater Occipital Nerve; ONS, Occipital nerve Stimulation; SUNA, short lasting unilateral neuralgiform headache attacks with autonomic features; SUNCT, short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

Table 2: Demographic data

Outcome Measure	Prior ONS (n=51)	Post ONS (n=51)	Percentage Change	Mean Difference (95%CI)	P Value
Whole Cohort					
Mean daily attacks (SD) Range	3.73 (±1.83) 1-8	2.12 (±2.28) 0-8	46.1% (±43.69) 0-100	1.61 (0.88, 2.34)	<0.001*
Mean attack intensity (SD) Range (VRS)	8.43 (±1.61) 5-10	6.17 (±3.54) 0-10	26.4% (±37.47) 0-100	2.27 (1.18, 3.35)	<0.001*
Mean attack duration (SD) Range (hours)	1.66 (±1.62) 0.3-10.5	0.85 (±0.98) 0.0-5.5	43.3% (±39.27) 0-100	0.801 (0.46, 1.15)	<0.001*
CCH Alone (n=32)					
Mean daily attacks (SD) Range	3.88 (±1.69) 1-8	1.91 (±2.10) 0-7	49.5% (±43.84) 0-100	1.96 (1.03, 2.90)	<0.001*
Mean attack intensity (SD) Range (VRS)	8.22 (±1.73) 5-10	6.64 (±3.20) 0-10	25.0% (±36.56) 0-100	1.57 (0.34, 2.81)	0.014*
Mean attack duration (SD) Range (hours)	1.54 (±1.05) 0.3-4.0	0.86 (±0.78) 0.0-2.8	43.2% (±38.46) 0-100	0.68 (±0.30, 1.06)	<0.001*
Multiple Phenotypes (n=19)					
Mean daily attacks (SD) Range	3.47 (±2.06) 1-8	2.47 (±2.59) 0-8	40.3% (±43.97) 0-100	1.00 (0.24, 2.24)	0.036*
Mean attack intensity (SD) Range (VRS)	8.79 (±1.34) 6-10	5.37 (±4.00) 0-10	28.8% (±39.83) 0-100	3.42 (1.32, 5.51)	0.003*
Mean attack duration (SD) Range (hours)	1.84 (±2.32) 0.3-10.5	0.848 (±1.27) 0.0-5.5	43.5% (±41.70) 0-100	0.99 (0.28, 1.71)	0.009*

CCH, chronic cluster headache; CI, Confidence interval; ONS, Occipital nerve Stimulation; SD, Standard deviation; VRS, verbal rating scale

Table 3: Summary of attack outcome measures

	Pre-ONS	Post-ONS	Change in score	P value
Whole Cohort (n=51)				
MIDAS (n=51) Mean (±SD) Range	149.84 (±89.10) 0-270	114.92 (±106.66) 0-270	34.92 (±100.19)	0.016*
HIT-6 (=51) Mean (±SD) Range	67.73 (±6.08) 53-80	60.68 (±13.07) 10-78	7.05 (±11.08)	<0.001*
HAD-A (n=51) Mean (±SD) Range	12.16 (±5.005) 1-21	10.12 (±5.41) 0-21	2.04 (±5.63)	0.013*
HAD-D (n=51) Mean (±SD) Range	12.04 (±4.68) 1-21	9.22 (±6.10) 01-21	2.82 (±5.56)	0.001*
BDI-II (n=49) Mean (±SD) Range	27.59 (±14.45) 0-55	22.82 (±15.98) 0-56	4.77 (±13.66)	0.018*
EQ5D (n=49) Mean (±SD) Range	0.69 (±0.11) 0.55-1.00	0.69 (±0.15) 0.18-1.00	0 (±0.11)	1.00
EQ-VAS (n=49) Mean (±SD) Range	49.75 (±23.24) 0-95	52.42 (±27.62) 5-95	-2.67 (±17.08)	0.285
SF-36 P (n=51) Mean (±SD) Range	32.12 (±9.97) 13.70-52.30	33.82 (±11.80) 11.80-55.70	-1.70 (±9.14)	0.191
SF-36 M (n=51) Mean (±SD) Range	34.14 (±12.97) 15.3-58.5	38.34 (±14.79) 14.70-62.70	-4.20 (±13.95)	0.036*

CCH alone (n=32)				
MIDAS (n=32) Mean (±SD) Range	156.25 (±91.19) 0-270	108.59 (±111.35) 0-270	47.66 (±108.65)	0.019*
HIT-6 (=32) Mean (±SD) Range	67.91 (±6.31) 53-80	60.28 (±14.04) 10-78	7.62 (±11.94)	0.001*
HAD-A (n=32) Mean (±SD) Range	12.81 (±4.30) 3-21	10.78 (+4.67) 0-19	2.03 (±5.43)	0.043*
HAD-D (n=32) Mean (±SD) Range	12.28 (±4.48) 1-20	9.47 (±6.02) 0-20	2.81 (±5.39)	0.006*
BDI-II (n=32) Mean (±SD) Range	28.34 (±14.23) 0-52	22.30 (±15.75) 0-53	6.43 (±11.67)	0.005*
EQ5D (n=30) Mean (±SD) Range	0.70 (±0.11) 0.55-1.00	0.70 (±0.13) 0.55-1.00	0.00 (±0.09)	0.908
EQ-VAS (n=30) Mean (±SD) Range	56.13 (±19.89) 20-90	55.00 (±24.25) 10-95	1.96 (±12.74)	0.405
SF-36 P (n=32) Mean (±SD) Range	33.52 (±9.40) 18.8-52.3	35.06 (±10.82) 11.80-53.20	-1.54 (±8.93)	0.337
SF-36 M (n=32) Mean (±SD) Range	33.99 (±13.38) 16.60-58.20	38.02 (±14.46) 14.70-62.70	-4.02 (±12.89)	0.087
Multiple phenotypes (n=19)				

MIDAS (n=19) Mean (±SD) Range	139.05 (±86.80) 8-270	125.58 (±100.28) 0-270	13.47 (±82.34)	0.485
HIT-6 (=19) Mean (±SD) Range	67.42 (±5.83) 58-78	61.32 (±11.58) 42-78	6.10 (±9.70)	0.013*
HAD-A (n=19) Mean (±SD) Range	11.05 (±5.96) 1-20	9.00 (±6.44) 0-21	2.05 (±9.70)	0.160
HAD-D (n=19) Mean (±SD) Range	11.63 (±5.39) 1-21	8.79 (6.38) 0-21	2.84 (±5.99)	0.053
BDI-II (n=19) Mean (±SD) Range	25.79 (±14.37) 5-55	23.63 (±16.74) 1-56	2.158 (±16.33)	0.572
EQ5D (n=19) Mean (±SD) Range	0.68 (±0.10) 0.55-0.84	0.68 (±0.17) 0.18-1.00	0.00 (±0.14)	0.925
EQ-VAS (n=19) Mean (±SD) Range	39.11 (±25.02) 0-95	49.50 (±33.09) 5-95	-10.38 (±20.71)	0.048*
SF-36 P (n=19) Mean (±SD) Range	29.77 (±10.70) 13.70-49.00	31.73 (±13.33) 13.70-55.70	-1.96 (±9.71)	0.390
SF-36 M (n=19) Mean (±SD) Range	34.38 (±12.61) 15.30-58.50	38.90 (±15.69) 14.80-59.50	-4.51 (±15.94)	0.233

BDI-II, Beck Depression Inventory II; CCH, Chronic cluster headache; EQ5D, Euro-QoL 5D Index; Euro-VAS, Euro-QoL visual analogue score; HAD-A, Hospital Anxiety and Hospital Depression Scores – Anxiety component; HAD-D, Hospital Anxiety and Hospital Depression Scores – Depression component; HIT-6, Headache Impact Test 6 Score; MIDAS, Migraine Disability Assessment Score; ONS, Occipital Nerve Stimulation; SD, Standard Deviation

Table 4: Summary of headache-related disability and mental state scores

	Adverse Event	Total Events
Hardware Related	Lead migration	1 (2%)
	Electrode erosion	2 (4%)
	ONS system revision	6 (12%)
	Rechargeable system	2 (4%)
	Lead revisions (lead tethering)	2 (4%)
	IPG revision secondary to pain	2 (4%)
	Explantation	4 (8%)
	Efficacy	3 (6%)
	Lead tethering causing neck pain	1 (2%)
	Battery depletion (Failure in under one year)	6 (12%)
	Battery replacement at any time	19 (37.3%)
Total Hardware Related Events		***38***
Biological	Infection *(superficial wound infection)* (surgical action n=0)	1 (2%)
	Pain over IPG/lead/wound sites (surgical action n=2)	12 (24%)
	Neck stiffness (surgical action n=0)	8 (16%)
	Allergy to surgical material	2 (8%)
	Wound site complication	3 (6%)
	Keloid scar	2 (4%)
	Idiopathic Urticaria	1 (2%)
	(surgical action n=0)	
Total Biological Related Events		***26***
Stimulator Associated	Undesirable changes in stimulation (surgical action n=0)	17 (33%)
Total Stimulator Associated Events		**17**
TOTAL		**81 events**

IPG, implantable pulse generator; ONS, Occipital nerve stimulator

Table 5: Adverse events

Study	Number of Patients	Mean age (years)	Chronic Duration (years)	Mean Number Preventatives Failed	Mean Follow-up [range] (months)	Patients improved >50%	Change attack Frequency	Change attack Severity	Change attack Duration	Preventative Treatment Reduction
Magis 2007[15],2011[12]	14	47.6	7.07	>4*	36.62 [11-64]	12/14 (86%)	-94.6%	+2.3 %	N/A	4/14
Burns 2007[16],2009[10]	14	44	6	>4**	17.5 [4-35]	10/14 (71%)	-33%	+8%	-23%	6/14 (triptans)
De Quintana 2010[17]	4	42	-	-	6+	4/4 (100%)	-56%	-48%	- 63.8%	3/14
Fontaine 2011[11]	13	44.6	9.8	>4*	14.6 [3-34]	10/13 (76%)	-68%	-49%	N/A	8/13
Mueller 2013[20]	24	30	-	>3	21.5 [4-47]	21/24 (88%)	-40%	-38%	N/A	- (40% reduction daily triptan dose)
Magis 2016[13]	10	47.6	7	>4*	71 [54-103]	9/10 (90%)	-70.8%	N/A	N/A	4/10
Leone 2016[10]	30	42	6.7	N/A	73.2 [2-11]	20/30 (66.7 %)	N/A	N/A	N/A	0
Our Study	**51**	**47.78**	**7.88**	**12.57**	**39.17 [2-81]**	**27/51 (52.9 %)**	**- 46.14 %**	**- 26.47 %**	**- 43.35 %**	**21/27† (26/51triptans)**

*As per ICHD definition of "intractable chronic cluster headache"; **Patients failed mean 9 preventatives in 2007 study; [+]No range given; †31 patients on preventative medication at implant

Table 6: Comparison of outcomes for occipital nerve stimulation in chronic cluster headache

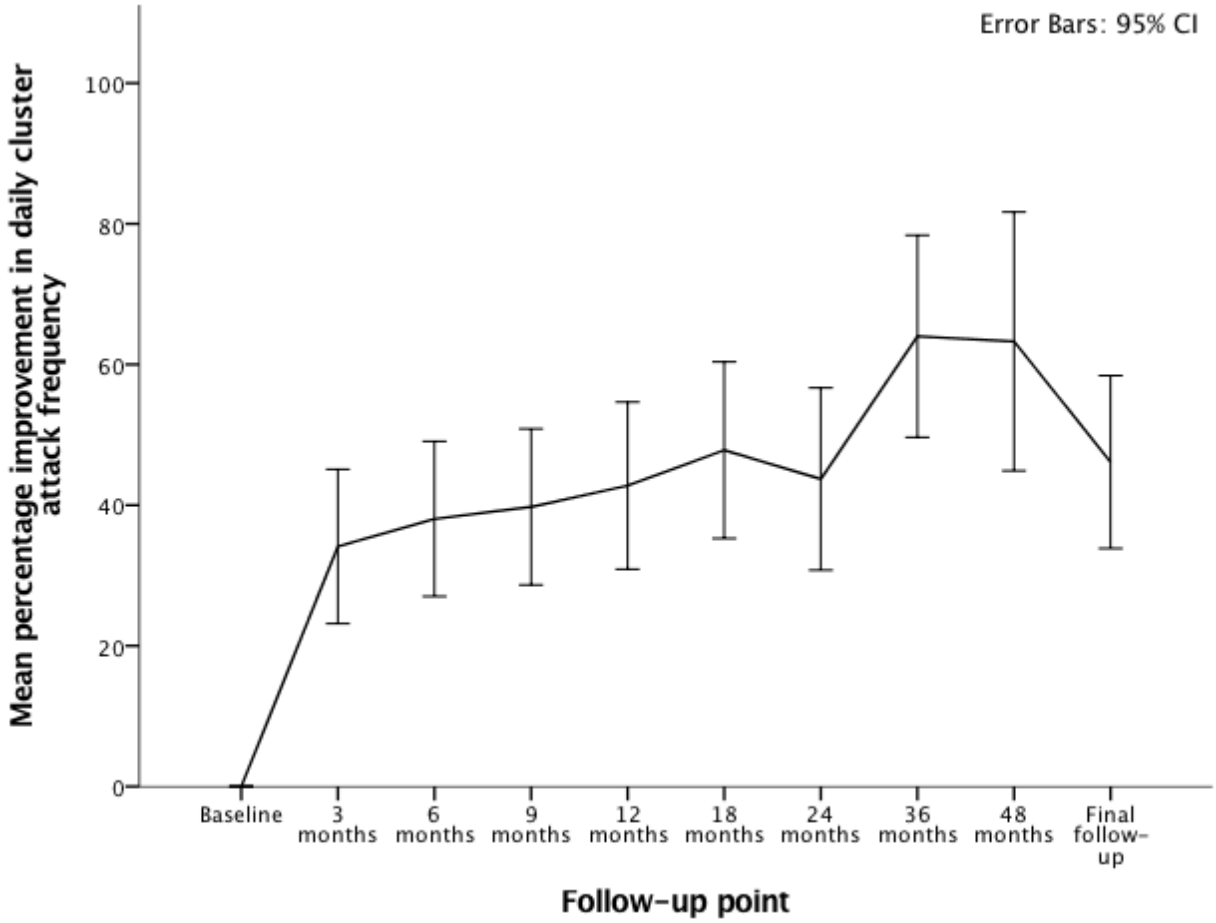
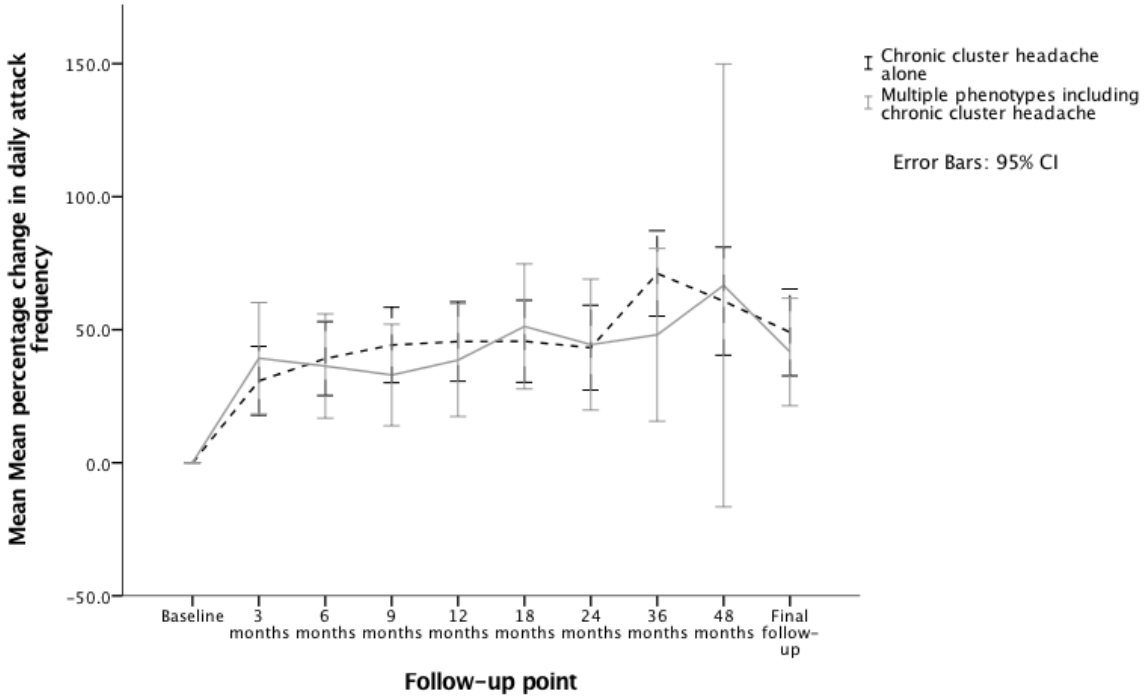


Figure 1a: Improvement of daily cluster attack frequency of entire cohort over follow-up



Follow-up (months)	Baseline	3	6	9	12	18	24	36	48	Final follow-up
CCH alone	32	32	31	31	31	28	24	21	16	32
Multiple Phenotypes	19	19	19	19	19	16	14	8	3	19
p-value	N/A	0.784	0.975	0.482	0.332	0.965	0.701	0.112	0.806	0.469

CCH, chronic cluster headache; N/A, not applicable

Figure 1b: Improvement in daily cluster attack frequency of those with chronic cluster headache alone compared to those with multiple phenotypes over follow-up. Table provides number of subjects included at each time point and p-value for difference in improvement between the groups.

Figure 1: Changes in improvement in daily cluster headache attack frequency following occipital nerve stimulation

	Number of patient who have tried drug (%)	Daily dose range (mg)	Mean maximum daily dose (mg)
Verapamil	51 (100)	240-1200	762
Lithium	49 (96.8)	200-2800	1014
Topiramate	39 (76.2)	25-800	232
Melatonin	39 (76.2)	4-15	13
Gabapentin	47 (92.1)	300-3600	2155
Pregabalin	34 (66.7)	150-1000	491
Valproate	35 (68.3)	50-3000	1110
Methysergide	46 (92.1)	2-27	9
Baclofen	9 (17.5)	10-90	57
Corticosteroid	36 (69.8)	-	-
IV DHE	44 (85.7)	-	-
GONB	48 (93.7)	-	-

GONB, greater occipital nerve block; IV DHE, intravenous dihydroergotamine;

Supplementary Table 1. Medications taken for cluster headache prior to occipital nerve stimulation

	Responders (n=27)					Non-Responders (n=24)				
	Pre-ONS		Post-ONS		P value	Pre-ONS		Post-ONS		P value
Headache Disability Scores										
MIDAS	N=27	153.11(±96.26)	N=27	79.04 (±101.36)	0.001*	N=24	146.17 (±82.21)	N=24	155.29 (±99.52)	0.581
HIT-6	N=27	67.04 (±5.68)	N=27	55.15 (±13.69)	<0.001*	N=24	68.50 (±6.54)	N=24	66.88 (±9.13)	0.343
Affect Scores										
HAD-A	N=27	12.19 (±4.89)	N=27	8.04 (±4.75)	<0.001*	N=24	12.13 (±5.23)	N=24	12.46 (±5)	0.786
HAD-D	N=27	11.11 (±4.93)	N=27	6.33 (±5.53)	<0.001*	N=24	13.08 (±4.52)	N=24	12.46 (±5).06	0.452
BDI-II	N=27	23.65 (±12.76)	N=27	14.92 (±10.84)	<0.001*	N=24	32.04 (±15.21)	N=24	31.74 (±16.33)	0.921
Quality of Life Scores										
Euro-QoL										
Euro-QoL	N=26	0.75 (±0.09)	N=26	0.75 (±0.13)	0.693	N=22	0.63 (±0.10)	N=22	0.62 (±0.13)	0.719
Euro-Scale	N=26	61.42 (±18.17)	N=26	68.12 (±19.17)	0.106	N=22	35.95 (±21.54)	N=22	38.86 (±24.58)	0.373
SF-36										
SFP	N=27	34.40 (±9.48)	N=27	37.72 (±11.66)	0.106	N=24	29.56(±10.07)	N=24	29.43(±10.55)	0.932
SFM	N=27	36.25 (±13.76)	N=27	44.69 (±13.31)	0.008*	N=24	31.64 (±13.49)	N=24	30.95 (±13.14)	0.933

BDI-II, Beck Depression Inventory II; HAD-A, Hospital Anxiety and Hospital Depression Scores – Anxiety component; HAD-D, Hospital Anxiety and Hospital Depression Scores – Depression component; HIT-6, Headache Impact Test 6 Score; MIDAS, Migraine Disability Assessment Score; ONS, Occipital Nerve Stimulation; SF-36, short form 36-item health survey. SF-36 subscales: PF, physical function; RP, role

physical; BP, bodily pain; GH, general health; VT, vitality; SF, social function; RE, role emotional; MH, mental health. SF-36 composite domains: SFP, physical component; SFM, mental component

Supplementary Table 2: Headache disability and quality of life scales by treatment response

	Responders (n=36)			Non-responders (n=27)		
	Pre-ONS	**Post-ONS**	**P-value**	**Pre-ONS**	**Post-ONS**	**P-value**
Mean daily attacks (SD)	3.89 (±1.98)	0.48 (±0.70)	<0.001*	3.54 (±1.67)	3.96 (±2.03)	0.253
Mean attack intensity (SD) [VRS]	8.94 (±1.31)	4.63 (±4.01)	<0.001*	7.85 (±1.74)	7.90 (±1.78)	0.858
Mean attack duration (SD) [hours]	1.59 (±1.06)	0.45 (±0.58)	<0.001*	1.74 (±2.11)	1.31 (±1.14)	0.111

B.

	Responder	**Non Responder**	**P Value**
Mean final patient estimate %	78.87 (±26.63)	25.63 (±29.57)	<0.001*
Maximum patient estimate %	88.37 (±19.61)	40.42 (±32.53)	<0.001*

C:

	Responders (n=36)			Non-responders (n=27)		
	Pre-ONS	**Post-ONS**	**P-value**	**Pre-ONS**	**Post-ONS**	**P-value**
Mean monthly triptan dose (SD) **Range**	33.78 (±28.11)	4.41 (±7.69)	<0.001*	40.25 (±36.72)	36.50 (±41.73)	0.467

Mean monthly triptan cost per-patient(SD) Range (£)	£692.44 (±576.20)	£90.35 (±157.69)	<0.001*	£825.13 (±752.74)	£748.25 (±855.64)	0.467

ONS, Occipital nerve Stimulation; SD, Standard deviation; VRS, verbal rating scale

Supplementary Table 3: Headache outcome measures (A), patient estimate of improvement (B) and triptan use(C) by response to occipital nerve stimulation