



Treatment of hemicrania continua by occipital nerve stimulation with a bion device: long-term follow-up of a crossover study

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Summary

Background Hemicrania continua (HC) is a primary headache that comprises persistent unilateral pain, is associated with cranial autonomic features, and is responsive to indometacin. Some patients are unable to tolerate this treatment or it is contraindicated; for these patients, the medical options for therapy are restricted. Occipital nerve stimulation (ONS) is an effective treatment for medically intractable primary headache, but only three cases of HC treated with ONS have been reported. Here, we report long-term safety and efficacy data for ONS in six patients with HC. ONS was provided by a unilateral neurostimulation device, known as a bion, which might be described as a second-generation ONS device.

Methods Six patients aged 18 years or older who were diagnosed with HC had a suboccipital bion device implanted ipsilateral to their headache and received continuous unilateral ONS. A crossover study design was used: the bion was on for the first 3 months, off for the fourth month, and on again during long-term follow-up. Detailed prospective headache diaries were kept for 1 month before implantation and for 5 months afterwards. Long-term data were obtained from patients' estimates of their outcome. The outcome of this study was assessed by a comparison of headache pain severity before and after ONS.

Findings At a median follow-up of 13.5 months (range 6–21 months), five of six patients reported sufficient benefit to recommend the device to other patients with HC. At long-term follow-up, four of six patients reported a substantial improvement (80–95%), one patient reported a 30% improvement, and one patient reported that his pain was worse by 20%. The onset of the benefit of ONS was delayed by days to weeks, and headaches did not recur for a similar period when the device was switched off. Adverse events were mild and associated with transient overstimulation.

Interpretation ONS appears to be a safe and effective treatment for HC, particularly when indometacin is not tolerated or is contraindicated. The bion device was well tolerated, easily inserted without significant morbidity, and is one-twentieth of the volume of current devices. Such miniaturised devices are a potential new option for treatment of HC.

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Introduction

Headache is one of the most common illnesses and can range in severity from mildly irritating (eg, during an upper respiratory tract infection) to profoundly disabling primary headache disorders, such as migraine and cluster headache.¹ Some patients with disabling headache are greatly burdened by their problem and their treatment is a substantial challenge for physicians.² During the past 5 years, there has been increasing interest in neurostimulation of the occipital nerve as a treatment for medically intractable primary headache.³ Here, we report the use of a miniaturised device to treat an uncommon form of headache, hemicrania continua (HC),⁴ although the simplicity of such a device might have implications for the treatment of headaches in general.

Occipital nerve stimulation (ONS) for headache is currently achieved with a subcutaneously implanted pulse generator, which comprises a battery that is

placed in the chest wall or abdomen and is attached to extension leads that are tunnelled to join electrodes placed across one or both occipital nerves. This method of stimulating the occipital nerve requires the electrode leads to traverse the neck and, as a result, one of the most common complications is lead migration.⁵ The bion is a rechargeable, self-contained, battery-powered, telemetrically programmable, current-controlled mini-neurostimulator with an integrated electrode and battery that are encased in a device that measures 27 mm by 3.3 mm and weighs 0.7 g. The lithium-ion battery is charged with an external device that contains electric coils, which create an electromagnetic field.⁶ The bion device has previously been used to stimulate the pudendal nerve to treat detrusor overactivity and to reduce urinary incontinence.^{7,8} An earlier model of the bion has been studied in post-stroke shoulder subluxation and knee function and pain in patients with osteoarthritis.⁹ The systematic

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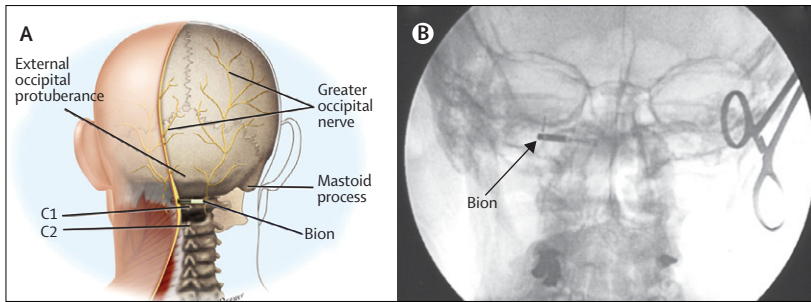


Figure 1: (A) Diagram and (B) intraoperative X-ray of bion in situ.

use of the bion to stimulate nerves in the occipital region to treat headache is novel, with previous uses only showing feasibility in migraine⁶ and in one patient with HC.¹⁰

ONS for primary headache has been studied most in migraine, for which there are more than 40 reported cases.^{11–13} In addition, there are two prospective, randomised, double-blind, placebo-controlled trials in progress (Precision Implantable Stimulator for Migraine [PRISM] and the Optical Nerve Stimulation for the Treatment of Intractable Migraine [ONSTIM] trial¹⁴). So far, 24 cases of chronic cluster headache have been treated with ONS,^{13,15–17} and 20 patients with chronic cluster headache have been treated with deep brain stimulation.^{18–20} The general message from these reports is that a substantial number of patients who are severely disabled or have medically intractable headache have excellent responses. However, as expected with any invasive therapy, there have been various side-effects, and the problems of the placebo effect and long-term outcomes are unresolved.

HC is a primary headache disorder, defined by the International Headache Society²¹ as a continuous, unilateral headache with exacerbations of severe pain that are associated with migrainous and cranial autonomic features and a complete response to therapeutic doses of indometacin.²² HC is a form of chronic daily headache, in which patients have 15 days or more of headache per month.²³ Peres and co-workers²⁴ have suggested that HC is not uncommon in clinical practice, owing to a 1-year prevalence of chronic daily headache in the general population of 4%²⁵ and the likelihood that many patients have not had an adequate trial of indometacin; however, our experience is that the disorder is relatively rare.²⁶ The pathophysiology of HC and the mechanism of the indometacin response are unknown;²⁴ furthermore, functional imaging studies show a unique pattern of brain activation in HC²⁷ compared with other primary headache disorders.²⁸ There is little information about the prognosis of HC. Of eight patients who were followed-up from a cohort of 34 new cases, three were pain free within 3–15 months, three could not tolerate indometacin and had headache recurrence, and two continued on

indometacin with partial relief.²⁹ The first patient was still taking indometacin at the time of death, many years after diagnosis.³⁰ The most important problem in the management of these patients is that other therapies do not consistently help; therefore, if patients develop gastrointestinal side-effects due to indometacin, their quality of life is substantially affected.

Three patients with HC have been treated with ONS, and all three benefited from the therapy.^{10,13} Our aim was to report on the safety, efficacy, and adverse events after long-term follow-up of six patients who were diagnosed with HC and were treated with a bion-type occipital nerve stimulator.^{8,9,31}

Methods

Patients

Patients who were diagnosed with HC in accordance with the International Headache Society classification²¹ and were outpatients at the National Hospital for Neurology and Neurosurgery, London, UK, were invited to participate in the trial. The National Hospital for Neurology and Neurosurgery receives referrals from neurologists throughout the UK. Patients were aged 18 years or older, stable on medication during the study period, and willing to follow the study procedures and complete diaries. Patients who could not tolerate or who had contraindications to indometacin were invited in preference to patients who were doing well on indometacin. The exclusion criteria were: intent to use an alternative therapy during the study; botox injections to treat headache within the past 90 days; previous destructive surgery that involved the C2 or C3 vertebrae or the trigeminal nerves; previous surgery in the vicinity of the implant; Arnold-Chiari malformation; participation in another trial of a device or drug within 30 days; intent to participate in another device or drug trial during the study period; pregnancy or intent to become pregnant during the study period; having another implanted electrical device, whether off or on; having passive implants that contain a large amount of metal or electrically conductive material, rostral to sternal notch (dental fillings were allowed); psychological or addictive behaviour; currently receiving or likely to receive diathermy; unresolved litigation with regard to head pain; another medical disorder that would confound the study; or the inability to operate the bion remote control or charging equipment, either themselves or by their caregiver. Written, informed consent was obtained from each patient or their caregiver before participation. Ethics approval to implant the bion device for chronic headache was obtained from the ethics committee of the National Hospital for Neurology and Neurosurgery, London, UK. Patients were not selected for this study on the basis of their response to occipital nerve block, and temporary cutaneous ONS was not used before the bion device was implanted.^{15–17}

For more on the **PRISM** trial see
[www.clinicaltrials.gov/
 NCT00286078](http://www.clinicaltrials.gov/NCT00286078)

For more on the **ONSTIM** trial
 see [http://www.clinicaltrials.gov/
 ct2/show/NCT00200109](http://www.clinicaltrials.gov/ct2/show/NCT00200109)

Procedures

Each bion device was implanted in an operating theatre at the National Hospital for Neurology and Neurosurgery, London. Patients spent four nights in the hospital, one of which was the night before surgery. A specially developed toolkit and a three-part, single-stage surgical procedure were used. First, anatomical landmarks were marked on the overlying skin in the occipitocervical region, with the patient sitting on a stool, and an image of the occipital region was obtained with an image intensifier (figure 1). The exact site to position the bion was localised by electrophysiological mapping of the occipital nerve. Patients were placed in the lateral position with the side of implantation lowermost, and a sterile field established. Local anaesthetic was infiltrated in the occipital region, with care taken to avoid anaesthetising the occipital nerve ipsilateral to the implant. Intravenous sedation was given, and a 3 mm incision was made in the dorsal surface of the neck in the midline at the level of the intermastoid line. A subcutaneous stimulating needle was inserted and passed towards the tip of the mastoid ipsilateral to the implant and advanced in 5 mm steps from the midline. The needle was connected to an external pulse generator to enable conduction of a stimulating current. The patient gave verbal feedback as to which position gave spreading occipital paraesthesia at the lowest stimulating current, and this optimum position was marked with a skin staple. Our understanding was that the amplitude of the current needed to produce paraesthesia, and therefore the rate of battery depletion, would depend on where the bion was placed relative to the occipital nerve. Preliminary mapping enabled the bion to be placed as close as possible to the greater occipital nerve, to minimise the stimulating current required.

The third part of the procedure was the insertion and deployment of the bion with the patient under intravenous sedation. Another 3 mm incision was made 3 cm from the midline on the side contralateral to the bion device at the level of the intermastoid line. A hollow delivery device, which was first loaded with a blunt trochar, was passed from the contralateral incision across the midline until its tip was just beyond the position marked with the skin staple. The blunt dissector was then removed, to leave the hollow introducer in place. The bion was held in a holding device and advanced through the introducer to the optimum position marked with the staple. The position of the bion was checked with an image intensifier (figure 1) before it was released and the implantation tools removed.

Postoperatively, the bion was activated on the day of implantation, and patients were instructed on the use of the external components: the remote control, charging (pillow) pad, and base station, which controls the charging field. A later addition was an updated,

smaller, and more portable charging pad known as the butterfly charger, which could be worn as a head band; this was used by all patients when it became available. Before the patient was discharged, anteroposterior and

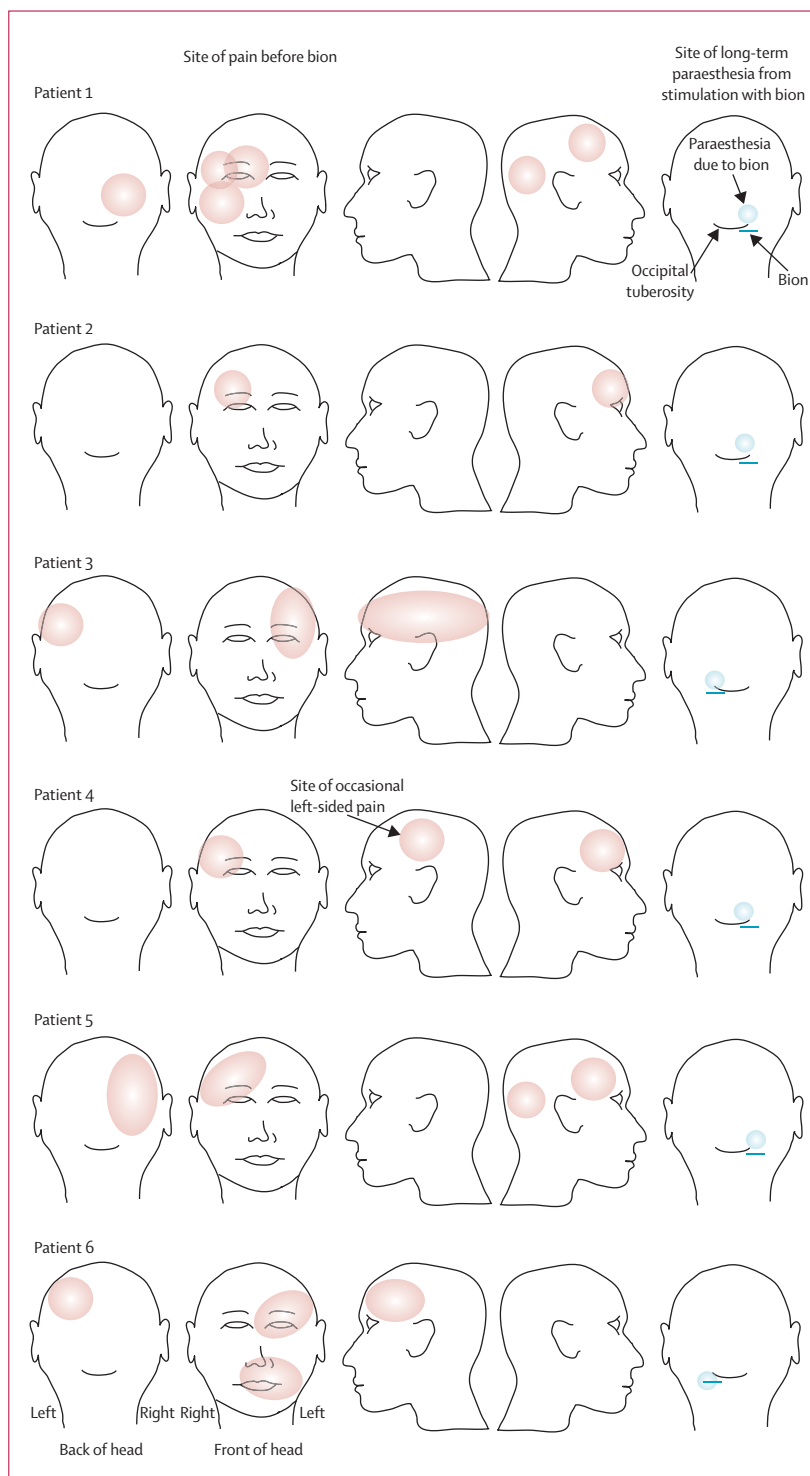


Figure 2: Sites of pain from HC and sites of long-term paraesthesia
The sites of pain from HC were the same after bion implants.

lateral radiographs of the craniocervical region were taken as a baseline record of the position of each bion. The bion was programmed with specially developed software to provide stimulation at a frequency of 60 Hz and pulse width of 250 µs for all patients; the amplitude of the bion current could be adjusted within a given range. Each bion was switched on and programmed to provide continuous stimulation for 3 months before it was switched off for the fourth month, which ensured the patients did not receive any stimulation of the occipital nerve. In month five the bion was switched on again and programmed as before.

The aim was to provide patients with paraesthesia that spreads upwards from the site of the electrode and felt comfortable. Patients were asked if they could feel paraesthesia at all times by varying the bion current if required. The bion has a range of 0–10 mA, and the minimum paraesthesia perception threshold for spreading paraesthesia and the discomfort threshold were tested in each patient at activation and during each follow-up session. We believed that the spreading paraesthesia was in the distribution of the occipital nerve and assumed that this showed stimulation of the occipital nerve that would equate with therapeutic efficacy. During the study, the investigators explained to patients that by keeping the amplitude of the bion current at the lowest level possible to maintain spreading paraesthesia, less power drainage from the battery would occur, resulting in less frequent charging.

Follow-up sessions were scheduled once per month for 4 months. Each follow-up session was attended by the patient, one investigator (BB), and a programming engineer from the sponsor. A single session typically lasted 1 h and during this the bion parameters were checked and, if required, advice about the use of the bion external controls or maintenance of the degree of stimulation-related paraesthesia was provided. Outside of scheduled visits, telephone contact was maintained as required, to provide technical assistance and advice. The maintenance of the pattern of paraesthesia was used as a way to check if the bion had moved out of position (figure 2).

Data were obtained for all the patients from handwritten diaries that contained a numerical pain severity scale with a range of 0–10 points (integers only) and hourly records were made prospectively during waking hours by each patient during the follow-up period. Patients were familiar with this type of diary because they had used similar ones for their indometacin tests.

We used the Migraine Disability Assessment Scale (MIDAS)³² to monitor disability during each follow-up and extended follow-up visit. This tool was primarily developed to assess disability in migraine and has been used extensively to assess primary headache disorders. MIDAS measures the burden of the disorder by quantifying how many full or at least half days are impaired by the disorder.

Baseline or preimplant data were obtained for 1 month (mean 28 days). Post-implant diaries were initially obtained for 4 months (mean 31 days per month), and all patients were willing to complete the diary in month five (mean 34 days, although some patients provided considerably more than 1 month of data) to record their response to switching the bion back on. The 5-month diary was returned to the investigators by post. The first patient recorded only 13 days of pre-implant diary data because he started the diary late, but his post-implant diary and those of the other patients contained between 28 and 41 days of entries, which showed the logistics of having the patient, investigator, and programming

	Age at implant (years)	Sex	Year of onset	Side of HC	Duration of HC at time of implant (years)	Date of implant	Length of follow-up (months)
1	55	Female	2000	Right	6	24/11/2006	9
2	64	Male	1971	Right	36	16/03/2007	6
3	49	Female	1973	Left	33	03/02/2006	18
4	37	Female	1988	Right	18	17/11/2006	9
5	60	Female	1998	Right	7	16/12/2005	20
6	54	Male	1995	Left	10	18/11/2005	21

Table 1: Characteristics of patients

	Indometacin test*	Oral indometacin use		
		Total daily dose	Response	Reason(s) for discontinuation of indometacin
1	Positive	150 mg	Improved	Dizziness and triggered a migraine-type headache
2	Positive	225 mg†	100 mg rectally was effective but 225 mg per day orally not effective	Rectal route of administration preferred because this prevented the patient waking at night due to headache
3	Positive	225 mg	Not tolerated	Abdominal pain and lethargy
4	Positive	150 mg	Improved	Still using 150 mg indometacin per day despite history of gastric ulcer and iron deficiency anaemia
5	Positive	225 mg	Improved	Dyspepsia
6	Positive	..	Not used because of gastroduodenitis	..

*Placebo controlled indometacin test with 100 mg or 200 mg indometacin. †Higher doses were not used. ..=not available or applicable.

Table 2: Responsiveness to indometacin

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Antidepressants	Amitriptyline Dosulepin	Amitriptyline Citalopram Dosulepin Fluoxetine	Amitriptyline Dosulepin Paroxetine Sertraline Venlafaxine	Amitriptyline	Amitriptyline	Amitriptyline Dosulepin Nortriptyline
β blockers		Propranolol		Propranolol		
Calcium channel blockers	Verapamil	Verapamil	Nifedipine Verapamil	Verapamil		
Antiepileptics	Gabapentin Topiramate Pregabalin	Carbamazepine Gabapentin Topiramate	Carbamazepine Gabapentin Topiramate Valproate	Topiramate	Gabapentin Valproate	Topiramate
NSAIDs		Aspirin (IV)* Aspirin (PO) Diclofenac Ibuprofen Naproxen	Diclofenac*	Aspirin (PO)* Ibuprofen	Diclofenac Ibuprofen Meloxicam*	
Selective COX2 inhibitors			Celecoxib Etoricoxib Rofecoxib	Celecoxib Rofecoxib	Celecoxib*	Celecoxib*
Triptans			Eletriptan Rizatriptan	Sumatriptan (PO)	Sumatriptan (PO)	Sumatriptan (SC)
Ergotamines		Dihydroergotamine	Dihydroergotamine Ergotamine	Dihydroergotamine Ergotamine		
Opioids		Codeine	Dihydrocodeine*		Codeine	Codeine
Other	Methysergide	Chlorpromazine (IM)* Melatonin Pizotifen	Lithium Prednisolone	Lithium Methysergide Paracetamol* Pizotifen Prednisolone*		Nefopam

*Of some benefit. NSAIDs=non-steroidal anti-inflammatory drugs. COX2=cyclo-oxygenase 2 inhibitors. IV=intravenous. IM=intramuscular. PO=orally. SC=subcutaneous.

Table 3: Previous drug or surgical treatment for headache by drug class

engineer available on the same day. Only full diary days were included in the analysis; therefore, we did not include the days each month when the patients attended for follow-up.

Assessments of mean headache severity were obtained at long-term follow-up from patients' estimates, to cover the period after they stopped recording in the diaries. At this stage, we also asked the patients to estimate their mean pain severity before starting the trial.

Statistical analysis

Each patient's monthly diary of hourly pain severities was divided into four periods, each lasting about 1 week, by dividing the number of complete days by four and keeping days whole. The median hourly pain-severity scores for each week were calculated with their IQR. Median pain severity scores were used to avoid assumptions about the relationship of the intra-individual pain severity scores. We used a generalised linear modelling approach, specifically the generalised estimating equations because the data were longitudinal.^{33,34} The daily pain level was deemed an ordinal dependent variable with a multinomial

distribution, with the nominal bion "on" or "off" variable and the ordinal study day variable to account for the baseline period (as within-patient variables) and fitted with an ordinal logistic link function (SPSS version 16). Microsoft Excel (2003) was used to obtain summary statistics and Sigma Plot (version 11) was used to display the results graphically. Patients' estimates of their own mean long-term pain severity before and after the bion was implanted were recorded as individual values. We asked the patients for their mean headache severity because this would be understood and was easier to provide than asking for the median, which was our preferred choice from the diary data.

Role of the funding source

The sponsor and PJG were involved in the initial design of the study. Recruitment of patients, data collection, data analysis, data interpretation, and writing of the report were done by the investigators. The sponsor was provided with a copy of the final report for information only. The authors had full access to all of the data, and the corresponding author had final responsibility for the decision to submit the manuscript for publication.

	Side of HC and side of injection	Injection in greater occipital nerve			Occipital nerve stimulation response	
		Year (number of injections)	Response	Duration of response	Response	Patient-determined overall estimate of improvement (%)
1	Right	2005 (1)	Improved	2 months	Positive	90%
		2005 (2)	No response	..		
		2005 (3)	Improved	3 weeks		
2	Right	2005 (1)	Improved	4 days	Negative	-20%
		2006 (2)	No response	..		
3	Left	2004 (1)	No response	..	Positive	95%
4	Right	2004 (1)	No response	..	Positive	30%
5	Right	2002 (1)	Improved	2 days	Positive	80%
		2002 (2)	Improved	3 months		
		2003 (3)	Improved	3 months		
		2004 (4)	Improved	3 months		
		2004 (5)	Improved	3 months		
		2005 (6)	Improved	Several months		
6	Left	2005 (1)	Improved	3 months	Positive	85%
		2005 (2)	Improved	3 weeks		

..=not available.

Table 4: Responses to injections in the greater occipital nerve with corticosteroid and lignocaine

Results

Six patients with HC (four women and two men) were recruited between October, 2005, and February, 2007; patients were followed-up for a minimum of 6 months after the bion was implanted. The median age at implantation was 55 years (range 37–64 years) and the median duration of the symptoms of HC was 14 years (range 6–36 years) at the time of implantation (table 1). All patients responded to indometacin but had had various problems with its use (table 2). Attempts were made to mitigate the effect of indometacin with proton-pump-inhibitors, indometacin suppositories, and cyclo-oxygenase 2 inhibitors; however, the patients only had modest improvement from these. Patients had previously used other treatments before or after diagnosis (tables 3 and 4). The sites of HC pain are shown in figure 2. During the period of follow-up, drug therapy was not altered to an extent that we suspected this had any influence on outcomes.

HC improved substantially with use of the bion in patients three, five, and six (figure 3), and the effect seemed to be incremental in these patients. As ascertained from the extended follow-up, these patients had a sustained and beneficial response and their estimated improvements were 80%, 85%, and 95%, respectively (table 5). Not only did these patients improve with the bion, but their pain got worse when the bion was switched off in month four and improved again when the bion was switched on in month five. This was the case even in patients who had symptoms for a long time before the bion was implanted (table 1). These three patients would recommend the bion to other patients with HC.

Patient one reported a 90% improvement at the time of long-term follow-up, although there was only a mild

improvement in the first 3 months and a slight deterioration in month four (figure 3). Since a few weeks into month five, there has been a consistent and prolonged improvement in her pain due to HC. She continued to have isolated cranial autonomic symptoms without pain. She would also recommend the bion to a patient in a similar position.

Patient four initially reported an improvement during the first 2 months (figure 3); this improvement returned almost to the baseline level before the bion was switched off for the fourth month. After 9 months' follow-up, she sleeps better at night because she wakes up in pain less often, and when the bion was switched off in month four, she noticed her sleeping was disturbed again. Overall, she reports a 30% improvement and would also recommend the bion to another patient.

Patient two reported a 20% worsening in his headache at 6 months, and would not recommend the device to other patients with HC.

There was a significant effect of the bion being on or off for the entire cohort (Wald $\chi^2=13.1$, $p=0.001$). We used a study-day term in the model to account for the baseline period ($\chi^2=0.01$, $p=0.92$). The results of this analysis suggest that the bion intervention reduces pain levels in this group. The overall estimated effect of the bion was a reduction in pain score of 5.8 points (95% CI 4.7–6.9 points).

The sum of baseline MIDAS scores for the six patients was 160 points, but this was reduced to 7 points at long-term follow-up (table 6), and patients three and six had substantial improvement. At baseline, patient six was not working owing to his headache, and after ONS he was able to return to work for 5 days per week. Patient three is a housewife, and she gained most

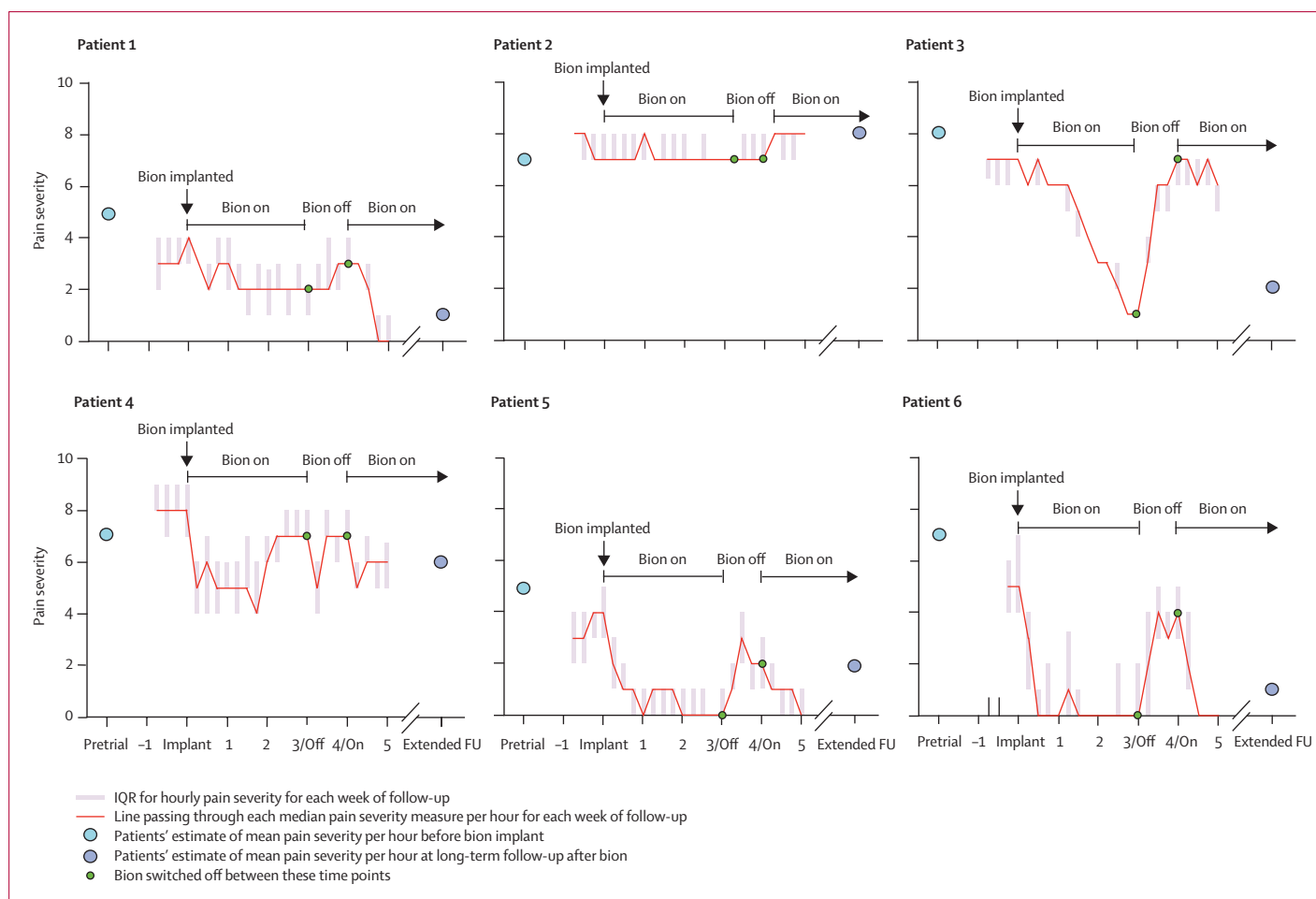


Figure 3: Individual outcomes during the study

Pain severity was assessed on a scale of 0–10 points (10 was the most severe), including the extended follow-up; follow-up visits at in months. FU=follow-up.

in terms of less disruption to household work. Patients four and five continue to work and do housework, despite their headache. Patient one was off work for reasons other than headache, and did household work despite her headache. Patient two was retired and continued with household work despite his headache.

The bion devices were well tolerated and they were activated on the same day as they were implanted. adverse events during follow-up were mild and when related to the bion they could be resolved in all cases. The main adverse event was the sensation due to overstimulation, during which the paraesthesia would become overly prominent under various circumstances (table 7). At long-term follow-up, one patient reported the recent onset of itchy hands and feet that was exacerbated during and for a short time after charging and might be related to starting omeprazole therapy.

Although this study did not set out to assess the following, they are deemed important enough to mention for future investigations. Delayed therapeutic responses before substantial improvement in the levels of pain due to HC were recorded in the hourly pain

severity diaries for patients three, five, and six. The beneficial response was delayed for a few days when the bion was first activated and then reactivated in month five for patients five and six; patient five did not have her first pain-free hours until 8 and 4 days after activation and reactivation, respectively, and patient six until 8 and 6 days after activation and reactivation, respectively. Moreover, when the bion was switched off in month four, patient five had her first day without any pain-free hours on day three, and after 6 days patient six had no more pain-free hours for the rest of that month. The beneficial response was also delayed for patient three, and she did not have her first pain-free hour until the end of month three after the bion was activated, and a similar amount of time after it was reactivated at the start of month five. However, substantial relief was obtained about halfway into month two, when typical pain severity was reduced from 7–8 points to 4 points. The deterioration for patient three, as for patients five and six, was delayed when the bion was switched off, but an increase in pain severity was evident by day two, although the pain did not reach prebion severity for

	Patients' estimate of HC (before)*	Patients' estimate of HC (after)†	Patients' overall view of HC pain severity since implant	Patients' estimate of change in HC since implant (%)	Patients' recommendation
1	5	1	Improved	90%	Yes
2	7	8	Worsened	-20%	No
3	8	2	Improved	95%	Yes
4	7	6	Improved	30%	Yes
5	5	2	Improved	80%	Yes
6	7	1	Improved	85%	Yes

*Mean pain severity of HC before bion (range 0-10) as assessed at time of follow-up. †Mean pain severity after bion at long-term follow-up (range 0-10).

Table 5: Patients' estimate of outcome and recommendations

	Before bion	1 month	2 months	3 months	4 months	Extended follow-up
1	13 points	7 points	0 points	0 points	8 points	0 points
2	7 points	9 points	6 points	4 points	0 points	0 points
3	45 points	50 points	43 points	20 points	36 points	0 points
4	1 points	0 points	0 points	0 points	0 points	0 points
5	18 points	11 points	0 points	0 points	3 points	0 points
6	76 points	73 points	68 points	60 points	57 points	7 points

Table 6: Migraine Disability Assessment Scores (MIDAS)

	Up to 4 months	Longer than 4 months
1	Overstimulation (paraesthesia was overly prominent) when head was in neutral position, when passing through shop anti-theft device, and bending forward; pain at site of implant	..
2
3	Overstimulation on train; ipsilateral eye lacrimation	Occasional brief sensation of shock during charging
4	Overstimulation when charging, travelling in a car, and bending forward; bion out of charge (period of time without stimulation as bion was switched off)	Overstimulation led to vertiginous feeling, which was resolved after reducing amplitude of the bion
5	Exacerbation of gritty feeling in right eye (not resolved); transient lightheadedness and palpitations on 2 days (no recurrence and not bion related); painful ipsilateral shoulder (exacerbated by arthritis and not bion related)	Fluctuating gritty feeling in right eye not deemed to be related directly to the use of the bion
6	..	Itchy hands and feet bilaterally over past 68 weeks during bion charging and for a short time after, although the relation to the bion was not clarified; probably related to a drug reaction, although observations are ongoing

Adverse events were resolved unless specified. ..=none specified.

Table 7: Adverse events

16 days. Figure 3 shows the delayed responses for improvement and deterioration.

Although patient one had improved by 85% at the time of long-term follow-up—median pain severity was reduced from 4 points to 1 point—this improvement was only noticed 3 weeks after the bion was reactivated in month five and was not present during the first 4 months. The patient had not had such a prolonged improvement in the 6 years since she began

to have HC.

Table 4 shows the efficacy responses of greater occipital nerve block and ONS. The response to occipital nerve block with corticosteroid and lidocaine did not consistently predict the response to ONS.

Discussion

In this systematic prospective study of the bion device, four of six patients with disabling HC reported an improvement in symptoms of 80% or more. These data provide long-term, albeit open-label, evidence that ONS might have a role in the treatment of HC, particularly for those patients who develop side-effects or in whom indometacin is contraindicated. These data also show the potential of neurostimulation-based approaches for the management of disabling primary headache disorders. The bion device is the size of two matchsticks, it has little or no associated morbidity, and with careful placement seems to avoid lead migration, which is a problem with the current approaches.

Because the patients had long histories of HC, and three of the six patients had a clear inverse relationship between ONS and pain severity, the outcomes are likely to be more than a placebo effect. Because HC is a continuous and unremitting disorder, substantial contrasts between pain-free and pain-experiencing days could be recorded. The duration of follow-up shows that the beneficial response seems to be long lasting, whereas a placebo effect would be expected to wane in light of the length of baseline history in these patients. The 30% improvement reported by patient four is a modest outcome but was enough for her to recommend the bion to another patient. This might be a placebo effect, which can certainly be long lasting with continued intervention in chronic daily headache.^{35,36} Patient two initially reported a worsening of his headache at the start of month four, when the bion was switched off, and so the report of a 20% worsening after 6 months cannot easily be explained; we have advised him to continue with stimulation at present. The improvement seen by patient one began 8–10 days after she had an ankle arthroscopy with a spinal anaesthetic 10 days into month five. Additionally, at this time, she began gradually to increase the dose of

her hormone-replacement treatment (HRT) patch from 25 to 100 µg/24 h over the next 2–3 months. However, later in 2007, the oestradiol concentration of her patch was lower than the concentration in January, 2007, and her gynaecologist believes that she had not been absorbing the HRT; therefore, the HRT cannot have accounted for the improvement in her headache. The spinal anaesthetic also seems unlikely to account for the improvement in her headache because there was a delay of 8 to 10 days after this procedure before the headache was substantially reduced and she became pain free.

Although the adverse events were mild, one of the patients still has itching that is exacerbated during recharging of the bion, although these symptoms are probably related to a drug reaction from omeprazole because they started the same month as the drug was introduced and have recently reduced substantially since the drug was stopped.

The results of this study are encouraging, but the study is small, without a blinded placebo arm, and patients were followed up in a tertiary headache centre over many months with an understanding that this device could help to treat headache. As with all studies of this design, a placebo effect should be considered. However, placebo-controlled studies of ONS are inherently difficult because of the paraesthesia the patients feel when their occipital nerves are stimulated; we have not been able to dissociate the paraesthesia from the therapeutic effect in any of our preliminary work. The recurrence of pain and similar outcomes with conventional ONS devices in cluster headache^{15,16} (eg, the pain returns when the devices malfunction) suggests that there is more to ONS than just a placebo effect. The authors of at least two studies are attempting to obtain double-blind, placebo-controlled data on the use of ONS in migraine (PRISM and ONSTIM¹⁴). The delay in onset and offset of effect that was repeated at month five suggests more than a simple placebo effect; patients were given no expectation of such timing. As we have established with a placebo-controlled crossover approach,²⁷ HC is typically a persistent, long-term condition, that can respond to indometacin treatment, and patients had failed to respond to other therapies before the prospect of the bion had been raised.

Schwedt and colleagues¹⁰ described a 44-year-old woman with a 12-year history of HC after a head injury who had to discontinue indometacin because of abdominal pain, dizziness, and nausea. She had a bion device implanted that was programmed to provide continuous stimulation, with a pulse width of 300 µs, a frequency of 45 Hz, and an amplitude of 3–7 mA. The patient had significant postoperative improvement in pain severity and reduced frequency of exacerbations. The patient reported episodes of autonomic activation without headache, which we also noted in patient one of our cohort. The same investigators went on to

describe two women, aged 35 years and 38 years, with HC who had discontinued indometacin after side-effects that included bleeding and nausea and vomiting.¹³ One patient had unilateral ONS and one had bilateral ONS with standard leads and stimulator. Overall, the pulse width used was 240–450 µs, and the frequency was 25–60 Hz. The devices were voltage led, which varied between 0.1 V and 6.7 V. Follow-up was at 13 months and 21 months, respectively. Both patients had responded to ONS: the number of days of pain reduced from 90 to 10 and 90 to 12, respectively, the severity reduced from 7.5 points to 7.0 points and from 7.5 to 3.0 points, and MIDAS score improved from 127 points to 6 points and 168 points to 13 points.³⁷

Unlike cluster headache³⁸ and short-lasting, unilateral neuralgiform attacks with conjunctival injection and tearing,³⁹ deep brain stimulation has not been used to treat HC, although functional imaging might suggest a degree of pathophysiological overlap with these headaches;²⁸ therefore, ONS could be deemed a therapy for resistant cases.

Although further studies with, when possible, blinded control arms are desirable, there are substantial implications for clinical practice if our results are reproduced. In light of the simplicity of these devices compared with the prospect of many years of pharmacological therapy, particularly in young patients, important questions arise. Would it be better to implant devices sooner rather than later in patients with HC who have relatively high indometacin requirements? Should ONS be studied in other indometacin-sensitive headaches, such as paroxysmal hemicrania?⁴⁰ Will the introduction of these second-generation and third-generation devices change the approach and indications for preventive treatments more broadly in other primary headaches, such as migraine? Such devices might one day be preferred to medication in some groups of migraineurs, particularly women of reproductive age. Miniaturised devices have the potential to change headache practice if they prove to be robustly effective because the usual problems of the side-effects of medicine will no longer apply.

ONS for primary headache was developed from its use in treating occipital neuralgia,^{5,41,42} a secondary headache. Electrodes that stimulate the occipital nerve were implanted ipsilateral to the headache pain, and this approach has also been used to treat primary headache,¹³ despite the possibility of side swapping. Since the occurrence of postoperative side swapping in a patient with chronic cluster headache who was treated with unilateral ONS at the National Hospital for Neurology and Neurosurgery, London,¹⁵ we have used bilateral electrodes to treat primary headache. However, at present, the bion can only provide unilateral stimulation, owing to technical issues that limit recharging to one bion in the same patient. We therefore

elected to enrol patients with unilateral headache for this study, and HC was chosen. Although we recognise that even HC can swap sides, this has not happened in any patients so far.

Compared with the current ONS devices with implanted pulse generators, tunnelled extension leads, and electrodes, the bion is much smaller and less surgically invasive. The bion was well tolerated in our patients and adverse events only comprised overstimulation, which could be resolved by reprogramming the implant. However, there are more long-term data for implanted pulse generators. In a recent review it was noted that a localised electrode and generator system that did not require tunnelled leads would probably solve the main problems of ONS (eg, lead migration, which affects up to 15% of cases and necessitates electrode revision or repositioning⁴³). Infection is another postoperative risk of ONS, and in the larger series reported, five of 52 patients acquired infections,^{11,12,44} although most researchers have not reported infections.^{10,13,15,16,45} Owing to the tunnelling of extension leads and electrodes, infection seems more probable with implanted pulse generators than with the bion. For the same reason, although postoperative pain and neck stiffness were reported by several investigators in studies of implanted pulse generators, these seem less likely to occur with the bion device.

In this study, we have reported not only a delay of days to weeks before the pain of HC decreased after bion activation, but also a delay to recurrence of pain after switching the bion off, although the delay was not consistent for all patients. We have previously reported the use of ONS for medically intractable chronic cluster headache¹⁵ and noted that some patients had a delay of several months before maximum improvement, and a delay of hours to days when stimulation was switched off. These responses differ substantially to those eight patients with chronic migraine who were treated with ONS and studied with brain imaging as their headache pain improved or worsened within 5–10 min of switching their ONS device on or off, respectively,⁴⁶ although the latter group was selected from a larger cohort for the study. In a practical sense, the delayed response prevents the use of temporary stimulator systems or trials of stimulation to predict response. The contrast between the time course for the HC responses here and in the patients with cluster headache previously reported,^{15,16} in comparison with patients with migraine, further suggests that the effects seen are not simply those of placebo but show real biological differences among headache types. Understanding of the mechanism and basis for these time courses will probably provide insights into the biological differences between the disorders.

Patients in this study mostly had pain in the trigeminal region, although occipital pain was also

reported. We did not map the sites of pain and paraesthesia in detail, unlike a recent study of patients with a mix of chronic headaches who were treated with bilateral ONS.⁴⁷ One of the most remarkable aspects of the response to ONS is the dissociation of the distribution of the peripheral paraesthesia and the distribution of the pain in HC. Patients have pain in the trigeminal, ophthalmic division, and C2 sensory root innervations, yet the stimulator produces only occipitocervical paraesthesia. This finding suggests that the effects are mediated centrally. The existence of an anatomical overlap between the trigeminal and cervical dorsal root afferents in the spinal cord and medulla has been shown experimentally.^{48–53} Thus, a functional trigeminocervical complex is used to explain the experimental findings and some clinical aspects of head pain.⁵⁴ In 1967, Wall and Sweet⁵⁵ described the “temporary abolition of pain in man” by neurostimulation in eight patients who had diseases of their peripheral nerves; the investigators noted that patients had immediate relief from pain, but in four patients this lasted for more than 30 min after only 2 min of stimulation, and the other four patients had prolonged effects that lasted from a few seconds to a few minutes after the stimulus. The principle of the gate control theory of pain,⁵⁶ combined with the physiological overlap of afferents in the trigeminocervical complex, might partly explain the delay in the recurrence of pain for the patients with HC. Another possible explanation is a central neuromodulatory effect, and the delay in onset implies a neuroplastic process. Either option, or indeed the combination, offer much scope for further study.

Five out of six patients with HC reported a worthwhile beneficial effect from ONS with a novel miniature stimulator system and would recommend the procedure to patients who are similarly affected. The benefit of ONS persisted for a median follow up of 13·5 months, and the adverse events were mild. The diary records for these patients show their delayed responses to ONS and the delayed increase in headache after switching off ONS, which suggests that neuroplasticity might have a role in the mechanism through which ONS achieves its therapeutic efficacy. These delays, the lack of response to many other therapies, and the clinical nature of the underlying condition suggest that we report more than a placebo effect of ONS. Neurostimulation for medically intractable headaches could open up opportunities for the treatment of highly debilitated patients and offer the potential for insights into the pathophysiology of these troublesome disorders.

Contributors

The study was the idea of PJG. LW did the procedures. Data collection, summary, analysis, and manuscript preparation was done by BB, LW, and PJG.

Conflicts of interest

LW and PJG are involved in clinical trials of neurostimulation therapy in headache that are sponsored by Medtronic. BB has no conflicts of interest.

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References

- Lance JW, Goadsby PJ. Mechanism and Management of Headache (7th edn); New York: Elsevier, 2005.
- Goadsby PJ, Schoenen J, Ferrari MD, Silberstein SD, Dodick D. Towards a definition of intractable headache for use in clinical practice and trials. *Cephalalgia* 2006; **26**: 1168–70.
- Goadsby PJ. Neurostimulation in primary headache syndromes. *Expert Rev Neurother* 2007; **7**: 1785–89.
- Matharu MS, Boes CJ, Goadsby PJ. Management of trigeminal autonomic cephalalgias and HC. *Drugs* 2003; **63**: 1637–77.
- Weiner RL, Reed KL. Peripheral neurostimulation for control of intractable occipital neuralgia. *Neuromodulation* 1999; **2**: 217–22.
- Rogers LL, Swidan S. Stimulation of the occipital nerve for the treatment of migraine: current state and future prospects. *Acta Neurochir* 2007; **97**: 121–28.
- Groen JC, Amiel C, Bosch JL. Chronic pudendal nerve neuromodulation in women with idiopathic refractory detrusor overactivity incontinence: results of a pilot study with a novel minimally invasive implantable mini-stimulator. *Neurol Urology* 2005; **24**: 226–30.
- Bosch JL. The bion device: a minimally invasive implantable ministimulator for pudendal nerve neuromodulation in patients with detrusor overactivity incontinence. *Urol Clin North Am* 2005; **32**: 109–12.
- Salter A-CD, Bagg SD, Creasy JL, et al. First clinical experience with BION implants for therapeutic electrical stimulation. *Neuromodulation* 2004; **7**: 38–47.
- Schwedt T, Dodick D, Trentman T, Zimmerman R. Occipital nerve stimulation for chronic cluster headache and HC: pain relief and persistence of autonomic features. *Cephalalgia* 2006; **26**: 1025–27.
- Popeney CA, Alo KM. Peripheral neurostimulation for the treatment of chronic, disabling transformed migraine. *Headache* 2003; **43**: 369–75.
- Oh MY, Ortega J, Bellotte JB, Whiting DM, Alo K. Peripheral nerve stimulation for the treatment of occipital neuralgia and transformed migraine using a C1-2-3 subcutaneous paddle style electrode: a technical report. *Neuromodulation* 2004; **7**: 103–12.
- Schwedt TJ, Dodick DW, Hentz J, Trentman TL, Zimmerman RS. Occipital nerve stimulation for chronic headache—long-term safety and efficacy. *Cephalalgia* 2007; **27**: 153–57.
- Goadsby PJ, Dodick D, Mitsias P, et al. ONSTIM: occipital nerve stimulation for the treatment of chronic migraine. *Eur J Neurol* 2005; **12** (suppl 2): 198.
- Burns B, Watkins L, Goadsby PJ. Successful treatment of medically intractable cluster headache using occipital nerve stimulation (ONS). *Lancet* 2007; **369**: 1099–06.
- Magis D, Allena M, Bolla M, De Pasqua V, Remacle JM, Schoenen J. Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. *Lancet Neurol* 2007; **6**: 314–21.
- Burns B, Watkins L, Goadsby PJ. Treatment of medically intractable cluster headache by occipital nerve stimulation: long term follow up 13 patients. *Cephalalgia* 2007; **27**: 1190 (abstr).
- Leone M. Deep brain stimulation in headache. *Lancet Neurol* 2006; **5**: 873–77.
- Schoenen J, Di Clemente L, Vandenheede M, et al. Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. *Brain* 2005; **128**: 940–47.
- Black D, Bartleson JD, Torgrimson SM, Davis DH. Two cases of chronic cluster headache treated successfully with hypothalamic deep brain stimulation. *Neurology* 2007; **68** (suppl 1): A307.
- Headache Classification Committee of The International Headache Society. The International Classification of Headache Disorders (2nd edn). *Cephalalgia* 2004; **24** (suppl 1): 1–160.
- Sjaastad O, Spierings EL. HC: another headache absolutely responsive to indomethacin. *Cephalalgia* 1984; **4**: 65–70.
- Welch KMA, Goadsby PJ. Chronic daily headache: nosology and pathophysiology. *Curr Opin Neurol* 2002; **15**: 287–95.
- Peres MF. Hemicrania continua. In: Goadsby PJ, Silberstein SD, Dodick D, eds. Chronic daily headache for clinicians. London: BC Decker Inc, 2005: 105–08.
- Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain* 2003; **106**: 81–89.
- Cittadini E, Matharu M, Goadsby P. HC: a case series of forty patients. *Neurology* 2008; **70** (suppl 1): A425.
- Matharu MS, Cohen AS, McGonigle DJ, Ward N, Frackowiak RSJ, Goadsby PJ. Posterior hypothalamic and brainstem activation in HC. *Headache* 2004; **44**: 747–61.
- Cohen AS, Goadsby PJ. Functional neuroimaging of primary headache disorders. *Expert Rev Neurother* 2006; **6**: 1159–72.
- Espada F, Escalza I, Morales-Asin F, Nasas I, Iniguez C, Mauri JA. HC: nine new cases. *Cephalalgia* 1999; **19**: 442.
- Sjaastad O. Chronic paroxysmal hemicrania, HC and SUNCT: the fate of the three first described cases. *J Headache Pain* 2006; **7**: 151–56.
- Shellock FG, Cosendai G, Park S-M, Nyenhuis JA. Implantable microstimulator: magnetic resonance safety at 1.5 Tesla. *Invest Radiol* 2004; **39**: 591–99.
- Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the Migraine Disability Assessment Score in a population-based sample of headache sufferers. *Cephalalgia* 1999; **19**: 107–14.
- Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986; **73**: 13–22.
- Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986; **42**: 121–30.
- Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Headache* 2005; **45**: 293–307.
- Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; **80**: 1126–37.
- Dodick DW, Schwedt TJ, Trentman TL, Zimmerman RS, Hentz J. Trigeminal autonomic cephalalgias: current and future treatments. *Headache* 2007; **47**: 981–86.
- Leone M, Franzini A, Cecchini AP, Broggi G, Bussone G. Stimulation of occipital nerve for drug-resistant chronic cluster headache. *Lancet Neurol* 2007; **6**: 289–91.
- Cohen AS, Matharu MS, Goadsby PJ. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA). A prospective clinical study of SUNCT and SUNA. *Brain* 2006; **129**: 2746–60.
- Newman LC, Goadsby PJ. The paroxysmal hemicranias, SUNCT syndrome, and hypnic headache. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. Wolff's headache and other head pain. Oxford: Oxford University Press, 2001: 310–24.
- Picaza JA, Hunter SE, Cannon BW. Pain suppression by peripheral nerve stimulation. Chronic effects of implanted devices. *Appl Neurophysiol* 1977; **40**: 223–34.
- Waisbrod H, Panhans C, Hansen D, Gerbershagen HU. Direct nerve stimulation for painful peripheral neuropathies. *J Bone Joint Surg Br* 1985; **67**: 470–72.
- Weiner RL. Occipital neurostimulation (ONS) for treatment of intractable headache disorders. *Pain Med* 2006; **7** (suppl 1): S137–39.
- Johnstone CSH, Sundaraj R. Occipital nerve stimulation for the treatment of occipital neuralgia—eight case studies. *Neuromodulation* 2006; **9**: 41–47.
- Slavin KV, Nersesyan H, Wess C. Peripheral neurostimulation for treatment of intractable occipital neuralgia. *Neurosurgery* 2006; **58**: 112–19.
- Matharu MS, Bartsch T, Ward N, Frackowiak RSJ, Weiner RL, Goadsby PJ. Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. *Brain* 2004; **127**: 220–30.

- 47 Trentman TL, Zimmerman RS, Seth N, Hentz JG, Dodick DW. Stimulation ranges, usage ranges, and paresthesia mapping during occipital nerve stimulation. *Neuromodulation* 2008; **11**: 56–61.
- 48 Kerr FWL, Olafson RA. Trigeminal and cervical volleys. *Arch Neurol* 1961; **5**: 69–76.
- 49 Kerr FWL. Central relationship of trigeminal and cervical primary afferents in the spinal cord and medulla. *Brain Res* 1972; **43**: 561–72.
- 50 Le Doare K, Akerman S, Holland PR, et al. Occipital afferent activation of second order neurons in the trigeminocervical complex in rat. *Neurosci Lett* 2006; **403**: 73–77.
- 51 Goadsby PJ, Hoskin KL, Knight YE. Stimulation of the greater occipital nerve increases metabolic activity in the trigeminal nucleus caudalis and cervical dorsal horn of the cat. *Pain* 1997; **73**: 23–28.
- 52 Bartsch T, Goadsby PJ. Increased responses in trigeminocervical nociceptive neurones to cervical input after stimulation of the dura mater. *Brain* 2003; **126**: 1801–13.
- 53 Bartsch T, Goadsby PJ. Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. *Brain* 2002; **125**: 1496–509.
- 54 Bartsch T, Goadsby PJ. Anatomy and physiology of pain referral in primary and cervicogenic headache disorders. *Headache Curr* 2005; **2**: 42–48.
- 55 Wall PD, Sweet WH. Temporary abolition of pain in man. *Science* 1967; **155**: 108–09.
- 56 Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965; **150**: 971–78.