Systematic Reviews referred by the NICE Interventional Procedures Programme on behalf of the NICE Interventional Procedures Advisory Committee (IPAC)

Title	**Stimulation of peripheral nerves for the treatment of refractory pain (including peripheral nerve field stimulation) – Addendum 1 (Revision 1)**
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Declared interests of the authors
The authors declare no potential conflict of interests

This addendum was produced at the request of NICE to include evidence identified through public consultation of related NICE draft guidance and an updated literature search carried out in December 2012. The addendum updates Section 6.2.1.1.1 *ONS for chronic/ transformed migraine* of the original systematic review.

6.2.1.1.1 ONS for chronic/transformed migraine [Highlighted area 1 for this report]

Chronic migraine was defined in the International Classification of Headache Disorder 2nd edition (ICHD-II) as "migraine headache occurring on 15 or more days per month for more than 3 months in the absence of medication overuse". Transformed migraine refers to chronic migraine that developed from episodic migraine with increasing headache frequency but decreasing severity of migraine features. This term was proposed after the publication of an earlier version of ICHD (ICHD-I), but was not formally adopted in ICHD-II. Both chronic migraine and transformed migraine have been used in the literature, sometimes interchangeably, and with or without specific exclusion of migraine associated with medication overuse. We use the term 'chronic migraine' in the rest of this report for consistency, but use it to include chronic or transformed migraine in the various manifestations.

Efficacy

Three manufacturer-sponsored multicentre, parallel group RCTs (Lipton et al. 2009, Saper et al. 2011, Silberstein et al. 2012),[1-3] that included a total of 364 patients, provided data on short-term efficacy. The Saper et al. study (n=67) and Silberstein et al. study (n=157) have been published in full [2;3] with the third trial published only as a conference abstract at the time of this report (Lipton et al. 2009).[1] In addition, one single-centre, crossover RCT (n=30) and five published case series with a total of 81 patients, were also located. The characteristics and key findings of these studies are summarised in Table A1. Furthermore, two ongoing, single-centre RCTs recruiting approximately 30 patients each were also identified.[4;5]

All three multicentre RCTs included an initial blinded phase of 12 weeks, during which patients received active or sham stimulation according to randomised allocation. The blinded phase was followed by an open label phase of one to three years during which participants in the sham control group also switched to active stimulation (and thus there was no control group for longer-term follow-up). Sample sizes ranged from 67 to 157. The Saper et al. study also included a third arm of medication management group, which could be regarded as an open-label control group given that the patients were already refractory to medication management.[2] The Lipton et al. study and the study by Silberstein et al. were conducted in the USA.[1;3] The majority of study centres in the Saper et al. study were also located in the USA, but it also included a centre from the UK (which contributed 12 of the 66 patients analysed at three months).[2] The single-centre crossover RCT (n=30, Serra & Marchioretto, 2012) was an open-label study conducted in Italy.[6] A group with ONS being switched on was compared to another group with ONS being switched off for one month, and then the groups

crossover. Patients in the 'off' group could switch their stimulation on if they had ≥30% worsening in the number of severity of migraine attacks, and they did so after an average of just under five days. All patients had their ONS switched on after the first two-month period and continued to be followed up for ten further months.

Trial stimulation was carried out in Silberstein et al., Lipton et al. and Serra & Marchioretto studies.[1;3;6] A good response was a criterion for inclusion in Silberstein et al. and Serra & Marchioretto [3;6] (at least 50% reduction in pain or adequate paresthesia coverage in the painful area) but not in Lipton et al.[1] Occipital nerve block was performed in the Saper et al. study prior to randomisation and a reduction of 50% in migraine pain was required for a patient to proceed to randomisation.[2] Eight of the patients who did not meet this response criterion were nevertheless included in an additional (not randomly allocated) 'ancillary group' and were implanted with a stimulator. The Saper et al. study included only chronic migraine patients without medication overuse.[2] Baseline migraine days per month were similar across the studies (between 20 to 23).

In the Saper et al. study, patients and outcome assessors were blinded with regard to allocation between ONS and sham control, but allocation to the medication management group could not be blinded.[2] The Saper et al. study was judged to be at unclear or high risk for detection bias (patients in the active stimulation group received a programmer for controlling their stimulator, whereas patients in the sham control group did not; and the medication management group was not blinded); high risk for attrition bias (drop out 15% [5/33] in ONS group, 6% [1/17] in sham control group, and 0% in medication management group); and outcome reporting bias (numerical data for the sham control group was not reported for Profile of Moods States, Migraine Disability Assessment [MIDAS], functional disability scale and SF-36, as difference was not statistically significant).[2] The Silberstein et al. study was judged to be of unclear risk for outcome reporting (results for Zung Pain and Distress Scale and quality of life mentioned in conference abstract[7] but not reported in the full-text paper) and blinding of patients (who had experience of paresthesia during trial stimulation) and study personnel (blinding not mentioned) and of low risk for other risk of bias domains. Quality assessment of the Lipton et al. 2009 study was hampered by paucity of published information in the conference abstract. It was described as double-blind but no further detail was provided.[1] The crossover RCT (Serra & Marchioretto, 2012) was judged to be at high risk of bias due to its open-label design, high level of contamination arising from the control group being able to switch on their stimulation and lack of a washout period.[6]

Table A1 Characteristics and main findings of published and ongoing RCTs and published case series of ONS for chronic migraine

RCT				
Study & country	**Comparison & sample size**	**Patient selection and trial stimulation; baseline characteristics**	**Outcome measures and results**	**Comments**
Saper et al. 2011 [2] (ONSTIM study) Multicentre, USA, Canada and UK Single-blind 12 weeks, open label 3 years (ongoing) NCT00200109	ONS vs. sham stimulation vs. medication management (vs. ancillary - ONS in patients not responding to occipital nerve block) 110 screened 67 randomised (+ 8 assigned) 61 (+5) analysed	Required at least a 50% reduction in migraine pain with occipital nerve block; those who did not respond received ONS in a non-randomised 'Ancillary' group. Mean age: 43 years Female: 80% Baseline migraine days per month: 20 ± 7.6	Reduction in headache days (in which overall headache pain intensity ≥3 out of 10) per month at 12 weeks: ONS (n=28) 27.0 ± 44.8% (6.7 ± 10.0 days) Sham (n=16) 8.8 ± 28.6% (1.5 ± 4.6 days) Medication (n=17) 4.4 ± 19.1% (1.0 ± 4.2 days) Ancillary (n=5) 39.9 ± 51.0% (9.1 ± 12.3 days) Responder rate (≥50% drop in headache days per month or a ≥3-point drop in pain intensity from baseline) at 12 weeks: ONS 39% (11/28), sham 6% (1/16), medication 0% (0/17), ancillary 40% (2/5)	Sponsored by Medtronic; high risk of detection bias, attrition bias and outcome reporting bias Also reported decrease in overall pain intensity, reduction in days with prolonged, severe headache per month, improvement in Profile of Moods States, functional disability, Migraine disability assessment (MIDAS) average grade, and SF-36
Silberstein et al. 2012 [3] Multicentre, USA Double-blind 12 weeks, open label 1 year	ONS vs. sham stimulation 268 assessed 177 received trial stimulation 157 randomised & analysed	Migraine headache according to ICHD-II with modifications using the Silberstein-Lipton diagnostic criteria for transformed migraine. A successful trial stimulation (at least 50% reduction in pain or adequate paresthesia coverage in the painful areas) was required. Mean age: 45 years Female: 79% Baseline migraine day per month: 21.6 ± 7.0	ONS vs. sham stimulation at 12 weeks Treatment responder (≥50% reduction in VAS pain): 17.1% vs. 13.5% (p=0.55) Achieved 30% reduction in VAS pain: 35% vs. 17% (p=0.02) Reduction in MIDAS scores: 64.6 vs. 20.4 (p=0.001) Reduction in number of headache days: 27% vs. 15% (p=0.008)	Sponsored by St. Jude Medical Neuromodulation
Serra and Marchioretto, 2012 [6] Single centre, Italy Open-label, cross-over (2 x 1 month), uncontrolled follow-up 1 year	ONS 'on' vs. 'off', crossover after one month; no washout period in between 34 enrolled 30 randomised 29 completed 1-year assessment	Required ≥50% reduction in the number or severity of migraine attacks within 15-30 days of trial stimulation. Mean age: 46 years Female: 76% Baseline migraine days per week: 5.8 ± 1.6	Arm A* / Arm B* / P value Headache days/week, median (inter-quartile range) 1-4 weeks A 'on', B 'off': 2.1 (1.2-3.3) / 6.3 (3.6-7) / <0.001 5-8 weeks A 'off', B 'on': 6 (4.2-6.3) / 2.3 (1.5-2.8) / <0.001 Headache severity, Numerical Rating Scale 0-10, median (inter-quartile range) 1-4 weeks A 'on', B 'off': 5 (5-6) / 7.5 (7-8) / <0.001 5-8 weeks A 'off', B 'on': 8 (7.5-9) / 6 (4-8) / <0.05 *Number of patients for individual arms was not stated	No external funding. Also reported (both arms combined) significant improvement from baseline in MIDAS scores and SF-36 scores and significant reduction in the use of NSAIDs and triptans.

Lipton et al. 2009 [1] (PRISM study) Multicentre, USA Double-blind 12 week, open label 1 year **[Conference abstract only]**	ONS vs. sham stimulation 179 screened 140 randomised 132 implanted 125 analysed	Included migraine with and without aura, and chronic migraine. Trial stimulation was performed but a good response was not an inclusion criterion. Mean age: not reported Female: not reported Baseline migraine days per month: 23 ± 5.4	Change from baseline in migraine days per month at 12 weeks (mean ± SD): ONS (n=63): -5.5 ± 8.7. Sham (n=62): -3.9 ±8.2 p=0.29	Sponsored by Boston Scientific; not fully published - unable to assess risk of bias
Goadsby 2011 [4] (PRISM UK study) Single centre, UK Double-blind 12 weeks, open label 1 year NCT00747812	ONS vs. sham stimulation 25 (estimated enrolment)	Information not available	Migraine frequency and severity Frequency of adverse events Medication use	Sponsored by Boston Scientific; **ongoing trial**
Caillon 2012 [5] (SENGO-CAM Study) Single centre, France Single-blind 14 days NCT01184222	ONS vs. sham stimulation 30 (estimated enrolment)	Migraine patients with medication overuse headache by non specific analgesics according to the ICHD-II diagnostic criteria who are admitted to hospital for medication withdrawal	Rate of headache-free patients, fourteen days after medication withdrawal Number of headache days during the 14 days withdrawal period Rescue medication used	Sponsored by Centre Hospitalier Universitaire de Nice ; **ongoing trial**

Case series

Study, country, sample size, follow-up	Patient selection & baseline characteristics	Outcome measures and results	Comments
Popeney & Aló, 2003 [8] USA (Texas), single centre, n=25, mean follow-up 18 months	All 25 consecutive patients responded to temporary bilateral occipital nerve blockade. All patients completed a successful 5- to 7-day trial of outpatient stimulation (no patient failed). 76% (19/25) reported symptomatic medication overuse ≥ 6 months. Mean age 45 years (range 31-65), 88% female, median duration of transformed migraine 10 years	Outcome measure / Pre / post / p value Headache frequency/90 days, mean (SD) / 75.56 (26.81) / 37.45 (7.49) / p<0.001 Headache severity (0-10), mean (SD) / 9.32 (1.28) / 5.72 (3.31) / p<0.001 MIDAS score, mean (SD) / 121 (56) / 15 (25.1) / p value not stated Disability grade: I – no or little, II – mild, III – moderate, IV - severe / 100% grade IV / 60% grade I, 4% grade II, 16% grade III, 20% grade IV / p value not stated • Positive responder (≥50% improvement in frequency or severity of headache): 88% (22/25) • ≥75% pain relief: 80% (20/25), ≥50% pain relief: 20% (5/25) • Percentage reduction in MIDAS disability score, mean (SD): 88.7 (1.72)	Retrospective data collection via chart review and telephone interview. Cylindrical electrodes. 60% used stimulation intermittently and 40% used it continuously.

Oh et al. 2004 [9] USA (Pittsburgh and Houston), two centres, n=10, follow-up at 1 month and 6 months	10 patients with transformed migraine were consecutively implanted. The patients had failed ≥3 modes of conservative treatment (medication, physical therapy, blockade), had temporary complete or near complete (≥70%) relief of pain with occipital local anesthetic field block, with psychological screening revealing no major behavioral, drug habituation, or significant unresolved issues of secondary gain. All 10 patients obtained immediate paresthesia and pain relief of >50% during 'on the table' trial. Mean age 52 years (range 41-83), 100% female, median duration of symptom 12.5 years	Patients' subject rating of % reduction of pain : • At 1 month: 90% (9/10) had excellent pain relief (>90% pain relief), 10% (1/10) had good pain relief (75-90% pain relief) • At 6 months: 80% (8/10) had excellent pain relief, 20% (2/10) had good pain relief	Follow-up was obtained in the implanting physician's office or by phone interviews. Dual paddle style electrodes The case series shared common investigators with Popeney & Aló, 2003 above. It was not clear whether any patients were included in both case series.
Brewer et al. 2012 [10] USA (Arizona), single centre, n=12 for migraine (total n=29 for the whole case series with various types of headache disorders), duration of treatment at follow-up 1 to 70 months	The case series included all patients who underwent a trial of ONS during 2002-2011 in a single centre. Patients who participated in industry-sponsored trials were excluded. Mean age 40 years (range 28 to 60), 100% female, duration of symptom not reported	Patients with migraine: ONS deemed successful by investigator: 5/12 (42%) All patients (mixed population, n=26), change from baseline (mean ± SD): Headache days (n=14): -12.8% ± 38.3% Headache severity (n=17): -24.0% ±31.5% MIDAS (n=6): -49.9 ± 68.2%	Retrospective data collection through a chart review and telephone survey.
Kiss & Becker, 2012 [11] Canada, single centre, n=10, median follow-up 33 months	Patients who met the inclusion criteria for the ONSTIM trial above (migraine refractory to medical management; had pain located in occipital or suboccipital region responding to occipital nerve block; without medication overuse) in a single centre Mean age 45 years (range 32 to 58), 80% female, duration of symptom not reported	Continuing use of ONS: 5/10 • Five patients had their system explanted at 7.2 to 33.9 months • Five patients continued to use ONS for 31.2 to 38.2 months after first implantation	All patients were enrolled in the ONSTIM trial (Saper et al. 2011) Prospective data collection (independent of the trial) focused on the location of headache, paresthesia evoked by ONS and complications Cylindrical electrodes.
Mammis et al. 2012 [12] USA, single centre, n=24 for migraine (total n=99 for the whole case series with various types of headache and craniofacial pain), follow-up 3 to 65 months (range).	The case series included all patients who underwent peripheral nerve stimulation trials for headache or craniofacial pain from a single centre between 2004 and 2011. Chart reviews were carried out and diagnoses were retrospectively classified according to ICHD-II.	For the 24 patients with migraine headache: Successful trial stimulation 21/24 (88%) Permanent systems still used at last follow-up: 19/21 (90%)	8/24 migraine patients were enrolled in the trial by Silberstein et al. 2012 [3] Cylindrical electrodes. 22% (17/76) of the patients who had permanent implantation received trigeminal branch stimulation with or without ONS.

Reduction in migraine days

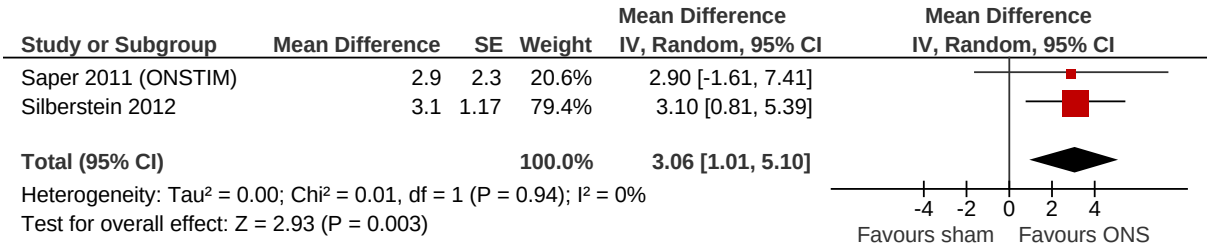
This outcome was measured and presented in various forms, with different definitions of migraine days (or headache days) adopted in different studies.

In the Saper et al. study, greater reduction in headache days (days with headache pain intensity ≥3) per month was observed in the ONS group (6.7 ± 10.0 days or 27.0% ± 44.8%) compared with the sham stimulation group (1.5 ± 4.6 days or 8.8% ± 28.6%) and medical management group (1.0 ± 4.2 days or 4.4% ± 19.1%) at 3-month follow-up. The difference between ONS and the two control groups were statistically significant ([calculated by EAC] ONS vs. sham, mean difference 5.20 days, 95% CI 0.86 to 9.54, p=0.02; ONS vs. medical management, mean difference 5.70, 95% CI 1.49 to 9.91, p=0.008).[2] Serra and Marchioretto reported a significantly lower headache days per week in the ONS 'on' group compared to the ONS 'off' group (median 2.1 vs. 6.3 for the first period before crossover, p<0.001).[6]

Popeney and Aló reported in their uncontrolled case series that a reduction in headache frequency per 90 days from a baseline of 75.56 (SD 26.81) to 37.45 (SD 7.49) was observed over a mean follow-up of 18 months (p<0.001).[7]

Reduction in days with prolonged, moderate/severe headache was reported in all three multicentre RCTs but with varied definitions (Silberstein et al.[3] – headache duration ≥4 hours with peak intensity reported as moderate or severe; Saper et al.[2] – days with prolonged, severe headache, not clearly defined; Lipton et al. conference abstract[1] – ≥4 hours of migraine with moderate/severe pain).The pooled result from the two fully published studies is shown in Figure A1.The pooled estimate suggested ONS reduces the number of days with prolonged moderate/severe headache by approximately three days per month (mean difference 3.06, 95% CI 1.01 to 5.10) compared with sham control and the difference was statistically significant (p=0.003). Inclusion of the result from the Lipton et al. conference abstract slightly reduces the between-group difference, which remains statistically significant (mean difference 2.59, 95% CI 0.91 to 4.27).

Figure A1 Mean reduction in the number of days with prolonged moderate/severe headache per month for ONS compared to sham control at 12 weeks



Lipton et al. stated in their conference abstract that in a pre-specified subgroup analysis for this outcome, a trend in favour of patients without medication overuse (ONS vs. sham, reduction of 5.9 vs. 2.6 migraine days/month) was observed compared with patients with medication overuse (ONS vs. sham, reduction of 5.0 vs. 4.8 migraine days/month).[1] Results for a formal test of interaction for the difference between subgroups were not presented.

Silberstein and colleagues reported significantly greater decrease in MIDAS score (which took into account both headache days and their impact on patient's life) at 3-month follow-up for the ONS group compared with sham control (64.6 vs. 20.4, p=0.001).[3]

Reduction in pain intensity

In the Saper et al. study, a greater reduction in overall intensity (0-10 scale) was observed in the ONS group (1.5 ± 1.6) compared with sham control (0.5 ± 1.3) and medical management (0.6 ± 1.0) at 3-month follow-up. The difference between the ONS group and the two control groups were statistically significant ([calculated by EAC] ONS vs. sham, mean difference 1.00, 95%CI 0.13 to 1.87, p=0.002; ONS vs. medical management, mean difference 0.90, 95% CI 0.14 to 1.66, p=0.02).[2] Silberstein and colleagues did not report mean reduction in pain intensity but they presented a 'continuous proportion responder analysis' based on pain intensity measured on VAS.[3] There was no significant difference in the proportion of patients who achieved at least 50% reduction in pain intensity between groups (17.1% for ONS vs. 13.5% for sham, p=0.55), which was the pre-specified primary outcome for this trial. However, a significantly higher proportion of patients achieved ≥30% reduction in pain intensity in the ONS group compared with the sham control (35% vs. 17%, p=0.02). Serra and Marchioretto (2012) reported a reduced severity of headache measured on the Numerical Rating Scale in the ONS 'on' group compared with the ONS 'off' group (median 5 vs. 7.5, p<0.001 for the first period before crossover).[6] Reduction in pain intensity was not reported in the abstract for the study by Lipton et al.[1]

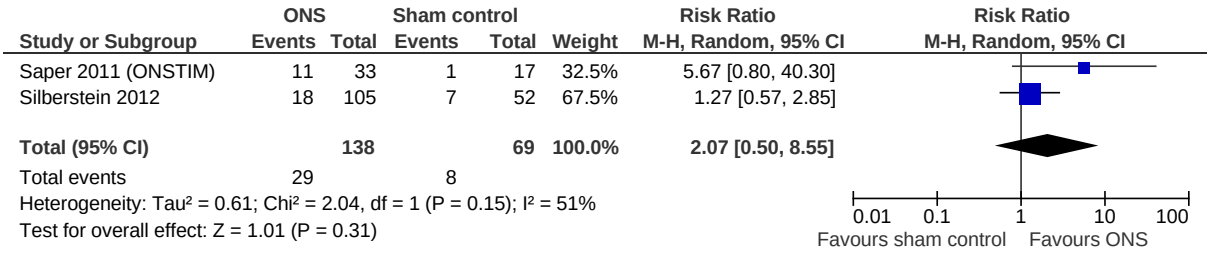
In a retrospective, uncontrolled case series, Popeney and Aló observed a significant reduction in headache severity (0-10 scale) from a baseline of 9.32 (SD 1.28) to 5.72 (SD 3.31) over a mean follow-up of 18 months ($p<0.001$).[8] In another retrospective, uncontrolled case series, Oh and colleagues reported that, at one month, 90% (9/10) of patients had excellent pain relief (>90% pain relief), while 10% (1/10) had good pain relief (75-90% pain relief). At six months, 80% (8/10) had excellent pain relief and 20% (2/10) had good pain relief. They stated that the pain relief was based on patient's subjective rating and was not measured using VAS.[9]

Responder rate

Responder was defined in the Saper et al. study as ≥50% reduction in headache days per month or a ≥3-point reduction in pain intensity from baseline. At 3-month follow-up, responder rate was 39% (11/28) for ONS group, 6% (1/16) for sham control and 0% (0/17) for medical management. The authors stated that the difference between ONS and the two control groups was statistically significant (p value not given).[2] However, the difference just failed to reach statistical significance when the data were analysed according to intention to treat assuming patients who dropped out were non-responders ([calculated by the EAC] ONS vs. sham control, RR=5.67, 95%CI 0.80 to 40.30, p=0.08; ONS vs. medical management, RR=12.18, 95%CI 0.76 to 194.94, p=0.08).

Responder was defined as ≥50% reduction in average pain intensity measured by VAS with no increase in average headache duration in the Silberstein et al. study.[3] As described earlier (under pain intensity), there was no significant difference between ONS and sham control at 3 months. Figure A2 shows the pooled result for the two trials. There was no significant difference between ONS and sham control (RR=2.07, 95%CI 0.50 to 8.55), and the statistical heterogeneity between the studies was high (I^2=51%).

Figure A2 Responder rates for ONS compared to sham control at 12 weeks



Popeney and Aló reported a response rate (50% improvement in frequency or severity of headache) of 88% (22/25) in their uncontrolled case series.[8] ONS was judged to be successful (define as ≥50% overall benefit as reported by patients in the telephone interview or records of the most recent clinic visit suggesting significant improvement) by the study investigators in 42% (5/12) of the patients in the Brewer et al. case series.[10]

Lipton et al. (conference abstract) investigated potential predictors for treatment response. They reported that in the ONS arm, a favourable response to the percutaneous trial stimulation was moderately predictive of 12-week response (positive likelihood ratio = 2.0, 95% CI 1.4 to 2.9; negative likelihood ratio = 0.21, 95%CI 0.06 to 0.78).[1]

Other outcomes

The Saper et al. study was described as a feasibility study.[2] Several other outcomes such as Profile of Moods States, MIDAS and SF-36 were measured although no primary endpoint was pre-specified. Overall, while the results were favourable for the ONS group compared to the sham control and medication management groups, the differences between groups were not statistically significant. The study also included a non-randomised 'ancillary' group that included patients who did not respond to occipital nerve block. Results suggested that these patients could still respond to ONS, but the number of patients (n=5) was too small to make any inference.

In the Silberstein et al. study, significantly more patients in the ONS group categorised their headache pain relief as 'good' or 'excellent' compared with the sham control group (p=0.001).[3] There was also significantly higher patient-reported percentage of headache pain relief in the ONS group (p=0.001).[3] Results for Zung Pain and Distress Scale and quality of life were mentioned in the conference abstract[7] of the study but were not reported in the published full-text paper.[3]

Serra and Marchioretto reported significant improvement from baseline in MIDAS (p<0.001) and SF-36 scores (p<0.05) at follow-ups at 1, 3, 6 and 12 months when data from the two trial arms were combined (i.e. analysed as an uncontrolled study).[6]

Safety

Detailed information on both device-related and non-device related adverse events were reported in the papers published by Saper et al.[2] and Silberstein et al.[3] Lipton et al provided

limited information on safety in their conference abstract.[1] In addition, safety data from five larger case series were also assessed.[8-12] Key findings from these studies are summarised in Table A2. Three of the case series included mixed populations of patients with various types of headaches and craniofacial pain. [9;10;12] Only information directly relevant to patients with chronic migraine is described in the main text here.

Serious adverse events

Three patients (6%) experienced serious adverse events requiring hospitalisation in the study by Saper et al.[2] These were related to implant site infection, lead migration and post-operative nausea. Silberstein and colleagues reported in their conference abstract two cases of serious device- or procedure-related events, including one case of infection and one case of post-operative pain that required hospitalisation.[7] Serra and Marchioretto stated that there were two severe implantation site infections and two severe lead dislocations in their case series,[6] whereas Kiss and Becker reported two cases of psychiatric complications requiring hospitalisations (one patient with pre-existing stable bipolar disorder required a 3-week hospital stay for narcotic addiction 10 months post implant; another patient with no prior psychiatric issues experienced significant depression requiring inpatient management).[11]

Lead migration/ dislodgement

Lead migration/ dislodgement was common across studies and there is some limited evidence to suggest using paddle leads rather than cylindrical leads can reduce occurrence rates. Occurrence of lead migration over three months ranged from 10% (5/52) of sham and 14% (15/105) of ONS in Silberstein et al RCT[3] study to 24% (12/51) of patients in Saper et al.'s RCT study.[2] Lead migration was not reported in Lipton et al. [1] In the crossover RCT by Serra and Marchioretto, there were three lead dislocations (3/30 - two severe, as described above; one mild) over one year.[6]

Among the case series, Popeney and Aló's reported 36% (9/25) lead migration over a mean follow-up period of 18 months.[8] In another retrospective case series Oh and colleagues reported that all seven patients initially implanted with cylindrical leads had lead migration within the first six weeks.[8] The patients were subsequently implanted with paddle leads with no further lead migration reported during follow-up.[9] Brewer and colleagues reported 75% (8/12) of patients having one to four revisions over a varied follow-up of 1 to 70 months,[10] whereas Kiss and Becker reported 40% 'loss of paresthetic coverage requiring revisions' over a median follow-up of 33 months. [11]

Measures were instigated during the trial by Saper et al. to reduce lead migration.[2] These included the use of circular coils when placing the lead extension to create strain-relief loops, and choosing the abdomen in preference of the buttock as the implant location for the neurostimulator where feasible. However, the impact of these measures was not reported.[2] Problems with performance of programming and of the lead were also reported in the Saper et al. study. [2]

Intraoperative failure

Saper et al report that 2 out of 53 patients had inadequate paresthesia over the location of pain during intraoperative testing and did not proceed to device implantation. [2]

Infection

Reported infection rates range between 4% and 30%. Infection at implant site for lead/extension tract and incision site complication was observed in the Saper et al. study in 14% (7/51) and 8% (4/51) of patients, respectively.[2] Silberstein et al. reported separately for ONS (4%, 4/105) and sham (6%, 3/52) in their study and one case required hospitalisation.[3] The Lipton et al. study (conference abstract) referred to infections being the most frequent device related adverse event. [3] Serra and Marchioretto reported one case of infection resulting in drop-out during trial stimulation and two severe implantation site infections (as described earlier) among 30 patients (7%) who were randomised and proceeded to permanent implantation.[6] Popeney and Aló reported 4% (1/25) infection over a mean follow-up period of 18 months.[8] There were two infections in Oh and colleagues' case series (2/10, 20%)[9] and one case of explantation due to infection in Brewer and colleague's case series of 12 patients.[10] Kiss and Becker reported three cases of 'inflammation at surgical sites' (3/10, 30%) that were treated with intravenous and oral antibiotics but stated that 'neither blood nor wound cultures identified bacterial growth'.[11]

Table A2 Summary of key safety findings of ONS for chronic migraine

Study, design & no. of patients implanted	Duration of follow-up	Failed trial stimulation	Serious adverse events (SAEs)	Lead migration (lead type)	Infection	Removal of stimulation system	Other adverse events (AEs)	Comment
Saper et al. 2011 [2] (ONSTIM), RCT, n=51	3 months	2/53	3/51 (6%) with SAE requiring hospitalisation: implant site infection, lead migration and postoperative nausea	12/51 (24%) cylindrical	Infection at the site of: Lead/extension tract 7/51 (14%) Neurostimulator pocket 2/51 (4%) See also SAE	Not reported	36/51 reported a total of 56 AEs Product ineffective: programming 6/51 (12%), lead 2/51 (4%) Incision site complication 4/51 (8%) Pain/discomfort at various sites	Reported adoption of various measures to reduce lead migration during the trial
Lipton et al. 2011 [1] (PRISM), RCT, n=132	2 years	Not reported	Not reported	Not reported	Listed among 'most frequent device-related AE'	Not reported	Non-target area sensory symptoms Implant site pain	**Conference abstract only**
Silberstein et al. 2012, [3] RCT, n=157	3 months Open label (result not yet reported) 24, 48 and 52 weeks	20/177	2 required hospitalisation and 49 additional surgery.	15/105 (14%) ONS and 5/52 (10%) for sham	Reported separately for ONS 4/105 (4%) and Sham 3/52 (6%)	4 (4%) of ONS withdrew due to AE	107 AEs reported. AEs are reported separately for ONS and Sham: Pain/discomfort at lead/pulse generator site 14/105 (13%) ONS and 9/52 (17.5%) Sham, wound complications 3 (3%) and 1(2%), skin erosion 4 (4%) and 2 (4%), allergic reaction 3 (3%) and 1 (2%), untended stimulation effect 6 (6%) and 1 (2%).	Also reported were case of diminished motor or musculoskeletal control in ONS and a case of subcutaneous tissue changes at implant site in the sham group.
Serra & Marchioretto 2012, [6] RCT, n=30	1 year	1/32	2 severe implantation site infections; 2 severe lead dislocations	3/30 (10%, 2 severe, 1 mild) cylindrical	2/30 (7%)[a] severe implantation site infections	Not reported	Stated that 'no adverse events led to long-term complications or nerve damage'.	Patients with infections exited the study; patients with lead migration had the electrodes re-positioned and no further complications occurred.
Popeney & Aló 2003, [8] case series, n=25	18 months (mean)	0/25	Not reported	9[b]/25 (36%) cylindrical	1/25 (4%)	1/25 (same one due to infection)	Not reported	Consecutive patients, retrospective

Oh et al. 2004,[9] case series, n=10[c]	Varied (≥ 6 months)	0/10	Not reported	7/7 (100%) cylindrical; 0/10 paddle	2/10 (20%)	1/10 (due to infection)	Not reported	Consecutive patients, prospective
Brewer et al. 2012,[10] case series, n=12 (migraine; whole case series mixed headache n=29)	Varied (1 to 70 months)	Mixed population 2/29	Not reported	8/12 (75%): two of the patients had 2 revisions and one had 4 revisions Lead type not reported	Mentioned one explantation for infection	Mentioned four explantation	Not reported	Consecutive patients, retrospective
Kiss & Becker 2012, [11] case series, n=10	33 months (median)	1/10[d]	Two psychiatric complications requiring hospitalisation.	4/10[e] (40%) cylindrical	3/10[f] (30%)	5/10	One delayed skin erosion 21 months after initial implantation One pulse generator malfunction requiring replacement at 17 months; the same patients reported intermittent non-painful swelling at the pulse generator and occipital sites	All patients were entrolled in the ONSTIM trial above
Mammis et al. 2012, [12] case series, n =24 (migraine; whole case series mixed headache and craniofacial pain n=99)	3 to 65 months (range)	3/24	Not reported	Mixed population: 5/76 (7%) necessitating revision	Mixed population: 6/76 (8%) requiring explantation and replacement [g]	Not reported	Mixed population: Overall rate of complication 15% Revision surgery 17/79 (22%)	

[a] One additional patient suffered infection during trial stimulation and was not randomised. [b] 6 were traumatic migration (related to motor vehicle accident or fall etc) and 3 were spontaneous migration. All were successfully repositioned. [c] This case series included 10 patients with transformed migraine and an additional 10 patients with occipital neuralgia. Results reported here are for the patients with transformed migraine unless otherwise specified. [d] One patient had inadequate paresthesia during the initial procedure but still had one lead implanted. [e] Loss of paresthetic coverage requiring revisions. [f] All three patients experienced inflammation at surgical sites and received intravenous and oral antibiotics but infections were not confirmed by bacteria culture and removal of stimulation system was not required. [g] Three following initial implantation and three following surgical revision.

Other adverse events

Other relatively common adverse events included pain and discomfort at various sites related to the procedure or implanted devices. Silberstein et al. report 13% of ONS and 17% of sham groups experienced persistent pain or numbness at lead or pulse generator site.[3] They also reported wound site complications (3% of ONS and 2% of sham), skin erosion (4% of ONS and sham) and allergic reactions (3% of ONS and 2% of sham). A single case of rash, hematoma and stitch abscess was reported in the study by Saper et al.[2] Kiss and Becker reported in their case series a delayed skin erosion 21 months after initial implantation and a pulse generator malfunction at 17 months along with a self-reported intermittent non-painful swelling at the pulse generator and occipital sites.[11]

Silberstein report 'lack of efficacy' in 2% (2/105) in ONS and 4% (8/52) in the sham and the occurrence of 'unintended stimulation effect' in 6% (6/105) of ONS and 2% (1/52) of sham.

Long-term complications or potential nerve damage

Saper and colleagues stated that there was no evidence of adverse device effects leading to long-term complications or potential nerve damage. Additionally there were no serious unanticipated adverse device effects reported or identified in the first three months of their trial.[2] A case of subcutaneous tissue change at implant site and another case of diminished or loss of motor or musculoskeletal control were reported in Silberstein et al. study.[3] Serra and Marchioretto stated that 'no adverse events led to long-term complications or nerve damage' in their crossover RCT of 30 patients over one-year follow-up.[6]

Summary and discussion: ONS for chronic/transformed migraine

- Evidence on efficacy was obtained from three industry-sponsored, multicentre RCTs (Lipton et al. 2009, Saper et al. 2011 and Silberstein et al. 2012),[1 2 3] including a total of 364 patients, one crossover, single-centre RCT of 30 patients (Serra and Marchioretto 2012) [6] and five case series covering a total of 81 patients.
- Two of the three industry-sponsored multicentre RCTs (Saper et al. 2011 and Silberstein et al. 2012), [1;3] including a total of 257 patients and the single-centre crossover RCT [6] have been published in peer reviewed journals. The third industry-sponsored RCT (Lipton et al 2009)[1] was only available as a conference abstract at the time of this report, limiting the available information for assessment of risk of bias and data synthesis. The risk of bias for Saper et al. study (n=67) was considered high with regard to attrition bias and outcome reporting bias.[2] Silberstein et al. study was considered to be low risk for selection bias, as it reported the use of computer generated

random sequences, and allocation concealment and for attrition bias, but risk of performance bias and reporting bias was unclear.[3] The crossover RCT was considered to be of high risk of bias due to its open-label design and crossover of the ONS 'off' group to the ONS 'on' group.[6] Assessment of success of blinding, or patients' expected effectiveness of treatment, was not mentioned in any of the trials.

- The duration of follow-up was relatively short (three months) for the blinded period of the parallel group RCTs. Long-term open-label follow-up of between one to three years is ongoing for some of the trials. Duration of follow-up varied in the case series and was up to 70 months.
- The majority of studies were carried out in the USA. One crossover RCT (n=30) was conducted in Italy and a case series (n=10) included patients from Canada. Only a single centre from the UK was included in one of the parallel group RCTs.
- The inclusion criteria with regard to medication overuse and the use of/response to trial stimulation or nerve block varied between studies.
- Significantly greater reduction in headache days (days with headache pain intensity $\geq$3) per month was observed in the ONS group (6.7 ± 10.0 days) compared with the sham stimulation group (1.5 ± 4.6 days, p=0.02 vs. ONS) and medical management group (1.0 ± 4.2 days, p=0.008 vs. ONS) at 3-month follow-up of the study by Saper et al. [2] Silberstein et al. reported significantly greater decrease in MIDAS score at 3-month follow-up for the ONS group compared with sham control (64.6 vs. 20.4, p=0.001).[3] The pooled result of Saper et al. and Silbserstein et al. studies suggests that ONS reduces the number of days with prolonged moderate/severe headache by approximately three days per month compared with sham control (mean difference 3.06, 95% CI 1.01 to 5.10, p=0.003).
- Patients in the ONS group in Saper et al. study experienced a significantly greater reduction in overall intensity (1.5 $\pm$ 1.6 on a 0-10 scale) compared with sham control (0.5 $\pm$ 1.3, p=0.002 vs. ONS) and medical management (0.6 $\pm$ 1.0, p=0.02 vs. ONS).[2] In Silberstein et al. study, there was no significant difference in the proportion of patients who achieved at least 50% reduction in pain intensity between groups (17.1% for ONS vs. 13.5% for sham, p=0.55), but significantly higher proportion of patients achieved ≥30% reduction in pain intensity in the ONS group compared with the sham control (35% vs. 17%, p=0.02).[3]
- There were no significant differences between the ONS group and the control group(s) in responder rates (which were defined differently in Saper et al.[2] and Silberstein et al.[3]) when analysed by intention to treat.

- Lead migration and infections are common and contributed to some of the reported serious adverse events. Lead migration occurred in 10% of patients in Sham (5/52) and 14% of ONS (15/105) in Silberstein et al. study,[3] 24% (12/51) of patients in Saper et al study over three months.[2] Serra and Marchioretto reported a similar rate of 10% (3/30) over one year in their crossover RCT.[6] Various and higher rates were reported in case series: 36% (9/25) over a mean follow-up of 18 months in Popeney and Aló,[8] 75% (8/12) over varied follow-up of 1 to 70 months in Brewer et al.,[10] and 40% (4/10) over a median follow-up of 33 months in Kiss and Becker.[11] The type of lead appears to determine the prevalence of migration with all seven cylindrical leads migrating in Oh et al. case series and none of the paddle lead placements.[9]
- Infection occurred at implantation sites in 14% (7/51) and 4% (2/51) of patients for leads/extensions and neurostimulators respectively over three months in the Saper et al. study.[2] Oh et al. reported an infection rate of 20% (2/10),[9] Kiss and Backer reported three cases (3/10, 30%) of inflammation at surgical sites (unconfirmed infections) treated with antibiotics.[11] A lower infection rate of 4 to 7% was reported in other studies (1/25 in Popeney & Aló et al.;[8] 4/105 in ONS and 3/52 in Sham in Silberstein et al.;[3] 2/30 in combined groups in Serra and Marchioretto[6]). Pain and discomfort at various sites related to implantation procedure and implanted devices were reported in the studies by Saper et al[2] and Silberstein et al.[3] No permanent nerve damage or unexpected serious adverse events were observed in Saper et al. and Serra and Marchioretto RCTs.[2;6]
- Methods for reducing lead migration including the use of strain-relief loops, choosing the abdomen in preference of the buttock as the implant location for the neurostimulator, and the use of a paddle lead instead of a cylindrical lead have been suggested.
- Findings from a subgroup analysis of the Lipton et al. study suggested that ONS may be more effective in patients without medication overuse compared to those with medication overuse.[1] Data from the trial also suggested that a positive response to trial stimulation may be predictive of subsequent treatment success. On the other hand, data from the Saper et al. study indicated that patients who did not respond to occipital nerve block may still respond to ONS.[2] These preliminary findings require further validation.

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Data table

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Silberstein et al. (2012)
Study type: Parallel group, double-blind, sham controlled RCT.
Country: USA (15 centres).
Study period: June 2005 to August 2010
Study population: Patients with chronic migraine.
n= 268 assessed, 177 received trial stimulation, 157 randomised, 153 completed 12-week assessment.
Mean age: 44.9 years
Sex: 79% female.
Mean duration of migraine headache: 22.8 years.
Inclusion criteria: patients who met the diagnostic criteria of migraine headache according to ICHD-II with modifications using the Silberstein-Lipton diagnostic criteria for transformed migraine, confirmed by one-month patient diary and who had a successful trial stimulation (defined as at least 50% reduction in pain or</td>
<td>
<table>
<tr><th>Results at 12 weeks</th><th>ONS (n=105)</th><th>Control (n=52)</th><th>P value</th></tr>
<tr><td>Treatment responder*</td><td>18 (17.1%)</td><td>7 (13.5%)</td><td>0.55</td></tr>
<tr><td>Achieved 30% reduction in VAS pain</td><td>35%</td><td>17%</td><td>0.02</td></tr>
<tr><td>Reduction in number of headache days</td><td>27.2%</td><td>14.9%</td><td>0.008</td></tr>
<tr><td>Reduction in MIDAS score</td><td>64.6</td><td>20.4</td><td>0.001</td></tr>
<tr><td colspan="2">Difference in reduction in headache days</td><td colspan="2">3.1 (95% CI 0.8 to 5.4) favours ONS</td></tr>
<tr><td colspan="2">Difference in reduction in MIDAS score</td><td colspan="2">44.1 (95% CI 22.8 to 65.3) favours ONS</td></tr>
</table>
*Treatment responder was defined as a patient who had a reduction from baseline of 50% or greater in average VAS pain intensity together with no increase in average headache duration

'Continuous proportion responder analysis' for mean daily average VAS pain intensity and for % reduction in headache days, patient-reported percentage of headache pain relief and categorical ratings of headache pain relief were
</td>
<td>
Adverse events (AEs)
107 AEs were reported. Two (2.1%) required hospitalisation and 49 (50.5%) required an additional surgery.
<table>
<tr><th>Results at 12 weeks</th><th>ONS (n=105)</th><th>Control (n=52)</th><th>P value</th></tr>
<tr><td>Lead migration</td><td>15 (14%)</td><td>5 (10%)</td><td>0.41</td></tr>
<tr><td>Persistent pain/ numbness at lead/ pulse generator site</td><td>14 (13%)</td><td>9 (17%)</td><td>0.63</td></tr>
<tr><td>Infection</td><td>4 (4%)</td><td>3 (6%)</td><td>0.69</td></tr>
<tr><td>Wound site complication</td><td>3 (3%)</td><td>1 (2%)</td><td>1.00</td></tr>
<tr><td>Skin erosion</td><td>4 (4%)</td><td>2 (4%)</td><td>1.00</td></tr>
<tr><td>Allergic reaction to surgical material</td><td>3 (3%)</td><td>1 (2%)</td><td>1.00</td></tr>
<tr><td>Unintended stimulation effect</td><td>6 (6%)</td><td>1 (2%)</td><td>0.43</td></tr>
<tr><td>Lack of efficacy</td><td>2 (2%)</td><td>4 (8%)</td><td>0.09</td></tr>
<tr><td>Withdrawal due to adverse event</td><td>4 (4%)</td><td>0</td><td>Not reported</td></tr>
</table>
Also reported a case of diminished or loss of motor or musculoskeletal control in the ONS group and a case of subcutaneous tissue changes at implant site in the sham group
</td>
<td>Study authors' overall conclusion: Although this study failed to meet its primary endpoint, it showed significant reductions in pain, headache days, and migraine-related disability. Additional controlled studies using endpoints that have recently been identified and accepted as clinically meaningful are warranted
Other outcome measures: Zung Pain and Distress Scale (PAD), quality of life and satisfaction with therapy were mentioned in the conference abstract but results were not reported in the paper
Risk of bias: See table below.
Stimulation device and parameters: Neurostimulation system (both leads and implantable pulse generator) was made by St. Jude Medical Neuromodulation. Lead type was not described. Leads were placed unilaterally or bilaterally. Genesis™ implantable pulse generator.</td>
</tr>
</table>

adequate paresthesia coverage in the painful areas) **Technique**: ONS vs. control (received a sham programmer with no stimulation delivered). **Follow-up**: Double-blind 4 &12 weeks; open label (results not yet reported) 24, 48, 52 weeks. **Conflict of interest**: Sponsored by St. Jude Medical Neuromodulation.	presented in figures in the paper.	From conference abstract: Rate of serious device- or procedure-related events was 1.0%, including one case of infection and one case of expected post-operative pain that required hospitalisation.	

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Serra and Marchioretto (2012)
Study type: Cross-over, open-label RCT.
Country: Italy (single centre).
Study period: Not reported
Study population: Patients diagnosed with chronic migraine with or without medication overuse headache
n= 34 enrolled, 31 underwent permanent implementation, 30 randomised, 29 completed one-year assessment.
Mean age: 46 years
Sex: 76% female.
Mean duration of migraine headache: not reported (mean age of onset 16 years)
Inclusion criteria: patients who had a diagnosis of chronic migraine or medication overuse headache and were refractory or intolerant to at least two prophylactic treatments; the number or severity of migraine attacks decreased by 50% within 15-30 days of trial stimulation.
Technique: ONS on vs. off; crossover after 4 weeks. Patients in the ‘off’ arm could switch on the stimulation if their headache attacks increased in severity or frequency by ≥ 30%. After two months all patients received active stimulation.</td>
<td>
<table>
<tr><th></th><th>Arm A*</th><th>Arm B*</th><th>P value</th></tr>
<tr><td colspan="4">Headache days/week, median (inter-quartile range)</td></tr>
<tr><td>1-4 weeks
A – on, B – off</td><td>2.1 (1.2-3.3)</td><td>6.3 (3.6-7)</td><td><0.001</td></tr>
<tr><td>5-8 weeks
A – off, B – on</td><td>6 (4.2-6.3)</td><td>2.3 (1.5-2.8)</td><td><0.001</td></tr>
<tr><td colspan="4">Headache severity, Numerical Rating Scale 0-10, median (inter-quartile range)</td></tr>
<tr><td>1-4 weeks
A – on, B – off</td><td>5 (5-6)</td><td>7.5 (7-8)</td><td><0.001</td></tr>
<tr><td>5-8 weeks
A – off, B – on</td><td>8 (7.5-9)</td><td>6 (4-8)</td><td><0.05</td></tr>
</table>
*Number of patients for individual arms was not stated

MIDAS scores (both group combined, n=29), median (inter-quartile range)
<table>
<tr><th></th><th>MIDAS total score</th><th>MIDAS - A</th><th>MIDAS - B</th></tr>
<tr><td>Baseline</td><td>79 (30-135)</td><td>70 (50-88)</td><td>8 (7-8)</td></tr>
<tr><td>1 month</td><td>27.5 (0-52)</td><td>25 (17-40)</td><td>6 (5-7)</td></tr>
<tr><td>3 months</td><td>19 (0-44)</td><td>20 (12-35)</td><td>6 (5-6)</td></tr>
<tr><td>6 months</td><td>10 (0-27)</td><td>19 (12-28)</td><td>6 (4-7)</td></tr>
<tr><td>12 months</td><td>10 (0-20)</td><td>14 (8-16)</td><td>5 (4-6)</td></tr>
<tr><td>P value</td><td><0.001</td><td><0.001</td><td><0.001</td></tr>
</table>
p<0.001 for each follow-up vs. baseline

SF-36 (both groups combined, n=29), mean ± SD
<table>
<tr><th></th><th>Physical component summary</th><th>Mental component summary</th></tr>
<tr><td>Baseline</td><td>42.9 ± 5.8</td><td>35.9 ± 8.2</td></tr>
<tr><td>12 months</td><td>45.4 ± 4.8</td><td>43.3 ± 5.8</td></tr>
</table>
P<0.05 for 12-months results vs. baseline
</td>
<td>Adverse events (AEs)
A total of 5 AEs were reported:
Two severe implantation site infections (one after trial stimulation and another prior to the 6-month follow-up) Both withdrew from the study and received required medical treatments. One patient asked to continue ONS treatment after recovery.
Three lead dislocations (2 severe, 1 mild). Electrodes were re-positioned and no further complications occurred.
Stated ‘no adverse events led to long-term complications or nerve damage.</td>
<td>Study authors’ overall conclusion: ONS appears to be a safe and effective treatment for carefully selected patients with chronic migraine and medication overuse headache.
Other outcome measures: proportion of days with headache attacks, individual components of SF-36
Risk of bias: high (see table below)
Stimulation device and parameters: INS, Synergy Versitrel (Medtronic). Extensions were placed in the neck area to form circular coils (acting as strain-relief loops). Parameter settings were variable according to patients’ need. A bipolar configuration was usually used. The stimulation frequency was 50 Hz; pulse width ranged between 330 μs and 450 μs; maximum stimulation amplitude 10.5 V.</td>
</tr>
</table>

<table>
<tr>
<td>Follow-up: 1, 3, 6 and 12 months following implementation.
Conflict of interest: declared no conflict of interest (no external funding).</td>
<td>Medication use (doses/month), both groups combined
<table>
<tr><th></th><th>NSAIDs (n=16)</th><th>Triptans (n=22)</th></tr>
<tr><td>Baseline</td><td>25.5</td><td>20</td></tr>
<tr><td>12 months</td><td>2</td><td>3</td></tr>
</table>
P<0.001 for 12-months results vs. baseline</td>
<td></td>
<td></td>
</tr>
</table>

Quality (risk of bias) assessment

Bias domain	Source of bias	Occipital nerve stimulation	
		Silberstein 2012	**Serra and Marchioretto, 2012**
Selection bias	Random sequence generation	Low	Unclear risk
	Allocation concealment	Low	Unclear risk
Performance bias	Blinding of participants	Unclear	High risk
	Blinding of study personnel	Unclear	High risk
Detection bias	Blinding of outcome assessment: patient reported outcomes	Unclear	High risk
	Blinding of outcome assessment: investigator assessed outcomes (adverse events)	Low	High risk
Attrition bias	Incomplete outcome data	Low	Low risk
Reporting bias	Selective reporting	Unclear	Low risk
Other bias	Any other important concerns about bias not covered in the other domains above	Unclear	High risk
	Measurement of effectiveness of blinding and/or patients' expectation of treatment effectiveness	No	No
Crossover design	Analysis of paired data	Not applicable	No
	Assessment of carryover effects and/or justification of washout period	Not applicable	No