OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

Anesthesiology and Pain Medicine
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Peer Review Report for "Peripheral Neuromodulation for the Management of Headache"

Author(s): Ivan Urits, Ruben Schwartz, Daniel Smoots, Lindsey Koop, Suhitha Veeravelli, Vwaire Orhurhu, Elyse M. Cornett, Laxmaiah Manchikanti, Alan David Kaye, Farnad Imani, Giustino Varrassi, Omar Viswanath

Review Timeline:

Submit Date: 21 Oct 2020
Revised Date: 2 Nov 2020
Accepted Date: 17 Nov 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | Revision (0) — 22 Oct 2020

Dear AE,
1- Please mention the number of narrative reviews that used in this study.
2- The method part should be revised in the abstract.
3- The manuscript should be arranged according to this journal instruction.
4- In the stem of the manuscript, the method part and method of data collection should be mentioned.
5- The manuscript needs to be edited again.
Thanks.

Amir-aziz Saif: Reviewer | Revision (0) — 23 Oct 2020

Dear AE,
The following recommendations are beneficial:
1) In the “abstract” section, there is not any information about the benefits and adverse effects of different modalities.
2) In “conclusions” it is preferable the authors mention that ultimately, which neuromodulation method seems supreme for management of common headaches (such as

migraine) with regard to its complications and side effects.
Thanks.

REFEREE: Reviewer | **Revision (0)** 25 Oct 2020

Dear AE,
Thanks for this review article titled " Peripheral neuromodulation for the management of headaches".
Despite the relatively acceptable substance of this manuscript, the publication of this article deserves serious consideration, since many revisions are required:
1. Please include a "methodology" to explain your search strategy in reviewed articles/devices.
2. The article is missing a "discussion" section to present authors' overall view of the discussed methods and results.
3. Please consult an English proofreading service. Quality of writing specially in sections under "Abstract", "introduction" and "limitations of Therapy" is fundamentally poor with numerous grammar and syntax errors, which considerably dissociate your article from publication in a scientific journal.
4. Please try to not focus on and minimize the use of commercial names (of the devices used in each model of therapy).
5. Under "Patient selection", although I agree with your statement that "headache is not a discriminatory pathology", the reviewed devices were tried in certain age population and not all. For example many of them (not all) are not approved to be used on children younger than 12.
6. There are many studies on evaluation of the efficacy of each device that you mentioned in your article. You may use those data to elaborate on the usefulness or limitations in using each device.
7. I believe it is better to eliminate statements like "… first medical device FDA approved... or … second device receiving FDA approved…". Again, I think it is better to use the scientific/generic format to introduce a device and not the commercial names. There are many companies that provide neuromodulation therapy. We try to stay neutral and to offer facts and to not advertise the name of any commercial companies (like Cefaly, etc.).
Thank you

REFEREE: Reviewer | **Revision (0)** 26 Oct 2020

Dear AE,
My comments are as below:
- The Word count is unacceptably high! Reduce it to a total of about 6000 counts.
- Describe the methodology.
- Write a discussion at the end of the paper.
- Limitation?
- Consider below three references:
Zhou L, Ashkenazi A, Smith J W, Jen N, Deer TR, et al. Long-Term Clinical Outcome of Peripheral Nerve Stimulation for Chronic Headache and Complication Prevention. Anesth Pain Med. 2016;6(4):e35983.
Buture A, Gooriah R, Nimeri R, Ahmed F. Current Understanding on Pain Mechanism in

Migraine and Cluster Headache. Anesth Pain Med. 2016;6(3):e35190.
Divizia M, Germani G, Urti I, Imani F, Varrassi G, et al. Endoscopic Neuromodulation of Suprascapular Nerve in Chronic Shoulder Pain: A Case Report. Anesth Pain Med. 2020;10(2):e103624.
Sincerely

REFEREE: Associate Editor | **Revision** (0) 26 Oct 2020

Dear EIC,
I read with interest this paper, and it has an attractive topic for publishing. Overall is acceptable, but based on reviewers' comments this submitted manuscript needs some corrections before publishing.
Final decision: Minor revision
Regards

REFEREE: EIC | **Revision** (0) 26 Oct 2020

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Journal: Anesthesiology and Pain Medicine

Manuscript ID: 110515

Title: Peripheral Neuromodulation for the Management of Headache

Dear Editor in Chief,

Thank you for your recent correspondence regarding our paper: **Peripheral Neuromodulation for the Management of Headache.**

It is our hope that the manuscript now meets the high standards of **Anesthesiology and Pain Medicine**. We also sincerely hope that this review will provide clinicians with relevant clinical information that will enhance both their clinical knowledge and patient care. Thank you again for the opportunity to revise our manuscript to this outstanding journal.

Specifically, with regard to your comments:

Reviewers' Comments:

Reviewer 1:

The following recommendations are beneficial:

1) In “abstract” section, there is not any information about benefits and adverse effects of different modalities. We have edited the abstract so it now reads:

Neuromodulation is an expanding field of study for headache treatment to reduce pain by targeting structures within the nervous system commonly involved in headache pathophysiology, such as the vagus nerve (VNS), occipital nerves, or sphenopalatine ganglion (SPG) for stimulation. Pharmaceutical medical therapies for abortive and prophylactic treatment, such as triptans, NSAIDs, beta-blockers, TCAs, and antiepileptics, are effective for some individuals, but

the role that technology plays in investigating other therapeutic modalities is essential. Peripheral neuromodulation has gained popularity and FDA approval for use in treating certain headaches and migraine headache conditions, particularly in those who are refractory to treatment. Early trials found FDA approved neurostimulatory implant devices, including *Cephaly* and *SpringTMS*, improved patient-oriented outcomes with reductions in headaches per month (frequency) and severity.

2) In “conclusions” it is preferable the authors mention that ultimately, which neuromodulation method seems supreme for management of common headaches (such as migraine) with regard to its complications and side effects. We appreciate this comment from the reviewer, however, we would like to refrain from suggesting which treatment is best and instead allow the reader to ascertain which treatment would be best for their patient from the evidence outlined for all of the treatments in this paper.

Reviewer 2:

1-Please mention number of narrative reviews that used in this study. We have updated the Evidence Acquisition to include our sources for this narrative review. This now reads: This was a narrative review. The sources for this review are as follows: Searching on PubMed, Google Scholar, Medline, and ScienceDirect from 1990-2019 using keywords: Peripheral Neuromodulation, Headache, vagus nerve, occipital nerves, sphenopalatine ganglion.

2-The method part should be revised in abstract. This has been updated. It now reads: This was a narrative review. The sources for this review are as follows: Searching on PubMed, Google Scholar, Medline, and ScienceDirect from 1990-2019 using keywords: Peripheral Neuromodulation, Headache, vagus nerve, occipital nerves, sphenopalatine ganglion.

3-The manuscript should be arranged according to this journal instruction. We arranged this

manuscript by filling in the exact template from the Anesthesiology and Pain Medicine journal website.

4-In stem of manuscript, the method part and method of data collection should be mentioned. We have added in this section. It now reads: This was a narrative review. The sources for this review are as follows: Searching on PubMed, Google Scholar, Medline, and ScienceDirect from 1990-2019 using keywords: Peripheral Neuromodulation, Headache, vagus nerve, occipital nerves, sphenopalatine ganglion.

5-The manuscript needs to be edited again. The entire manuscript has been edited again by trusted peers and grammatical editing software. We have made updates throughout that have been highlighted in red text.

Reviewer 3:

Thank you for your review article titled “ Peripheral neuromodulation for the management of headaches”.

Despite the relatively acceptable substance of this manuscript, publication of this article deserves serious consideration, since many revisions are required:

1. Please include a "methodology" to explain your search strategy in reviewed articles/devices. We have included this in the abstract. It now reads: This was a narrative review. The sources for this review are as follows: Searching on PubMed, Google Scholar, Medline, and ScienceDirect from 1990-2019 using keywords: Peripheral Neuromodulation, Headache, vagus nerve, occipital nerves, sphenopalatine ganglion.

2. The article is missing a "discussion" section to present authors' overall view of the discussed methods and results. We have added in a discussion section. This now reads: **Discussion**

Neuromodulation is an expanding field of study for headache treatment aimed at noninvasive therapy to reduce pain by targeting structures within the nervous system commonly involved in headache pathophysiology, such as the vagus nerve (VNS) or sphenopalatine ganglion (SPG) for stimulation (9). The first noninvasive neurostimulator device approved for migraine treatment was the Cefaly device. The Cefaly device is an external trigeminal nerve stimulation device (e-TNS) that transcutaneously excites the supratrochlear and supraorbital branches of the ophthalmic nerve (V1) via a bipolar self-adhesive electrode (30 x 94 mm) applied to the forehead. Larger randomized-controlled trials (RCT) are necessary to fully define the versatility of Cefaly eTNS application in migraine treatment. The second noninvasive neurostimulation device receiving FDA approval was the single-pulse transcranial magnetic stimulator, SpringTMS (sTMS). Similar to the evidence for eTNS, more rigorous randomized controlled trials are needed to elucidate the efficacy across the heterogenous migraineur population and long-term safety of sTMS. GammaCore is a handheld transcutaneous vagal nerve stimulator applied directly to the neck at home by the patient for treatment of cluster headache (CH) and migraine. GammaCore is not as widely studied in migraine, however, initial results have proven promising.

Several other non-FDA-approved devices are in development to treat headache and target headache evolution at different levels and inputs. They require more research in different age populations to be considered as prescribed treatments. The Scion device is a caloric vestibular stimulator (CVS) used for 20 minutes once or twice a day. The device interfaces with the user

through a set of small cones resting in the ear canal on either side and held in place by modified over-ear headphones. The sphenopalatine ganglion (SPG) has long been a target for headache treatment. The pulsante SPG Microstimulator is a device implanted in the upper jaw via an hour-long oral procedure. And finally, the occipital nerve stimulator (ONS). The device consists of an implanted pulse generator on the chest wall connected to a subcutaneous lead with 4-8 electrodes that is tunneled the occiput.

3. Please consult an English proofreading service. Quality of writing specially in sections under "Abstract", "introduction" and "limitations of Therapy" is fundamentally poor with numerous grammar and syntax errors, which considerably dissociate your article from publication in a scientific journal. The entire manuscript has been edited again by trusted peers and grammatical editing software. We have made updates throughout that have been highlighted in red text.

4. Please try to not focus on and minimize the use of commercial names (of the devices used in each model of therapy). We appreciate this comment from the reviewer but feel that it is necessary to include this information throughout the manuscript to be as clear as possible.

5. Under "Patient selection", although I agree with your statement that "headache is not a discriminatory pathology", the reviewed devices were tried in certain age population and not all. For example many of them (not all) are not approved to be used on children younger than 12. We thank the reviewer for this comment and we have added in statements throughout the paper to state that other age groups should also be included in future research.

6. There are many studies on evaluation of the efficacy of each device that you mentioned in your article. You may use those data to elaborate on the usefulness or limitations in using each device. We have elaborated on this in the discussion section which now reads: **Discussion**

Neuromodulation is an expanding field of study for headache treatment aimed at noninvasive therapy to reduce pain by targeting structures within the nervous system commonly involved in headache pathophysiology, such as the vagus nerve (VNS) or sphenopalatine ganglion (SPG) for stimulation (9). The first noninvasive neurostimulator device approved for migraine treatment was the Cefaly device. The Cefaly device is an external trigeminal nerve stimulation device (e-TNS) that transcutaneously excites the supratrochlear and supraorbital branches of the ophthalmic nerve (V1) via a bipolar self-adhesive electrode (30 x 94 mm) applied to the forehead. Larger randomized-controlled trials (RCT) are necessary to fully define the versatility of Cefaly eTNS application in migraine treatment. The second noninvasive neurostimulation device receiving FDA approval was the single-pulse transcranial magnetic stimulator, SpringTMS (sTMS). Similar to the evidence for eTNS, more rigorous randomized controlled trials are needed to elucidate the efficacy across the heterogenous migraineur population and long-term safety of sTMS. GammaCore is a handheld transcutaneous vagal nerve stimulator applied directly to the neck at home by the patient for treatment of cluster headache (CH) and migraine. GammaCore is not as widely studied in migraine, however, initial results have proven promising.

Several other non-FDA-approved devices are in development to treat headache and target headache evolution at different levels and inputs. They require more research in different age populations to be considered as prescribed treatments. The Scion device is a caloric vestibular stimulator (CVS) used for 20 minutes once or twice a day. The device interfaces with the user through a set of small cones resting in the ear canal on either side and held in place by modified over-ear headphones. The sphenopalatine ganglion (SPG) has long been a target for headache treatment. The pulsante SPG Microstimulator is a device implanted in the upper jaw via an hour-

long oral procedure. And finally, the occipital nerve stimulator (ONS). The device consists of an implanted pulse generator on the chest wall connected to a subcutaneous lead with 4-8 electrodes that is tunneled the occiput.

7. I believe it is better to eliminate statements like "… first medical device FDA approved... or … second device receiving FDA approved…". Again, I think it is better to use the scientific/generic format to introduce a device and not the commercial names. There are many companies that provide neuromodulation therapy. We try to stay neutral and to offer facts and to not advertise the name of any commercial companies (like Cefaly, etc.). We appreciate this comment from the reviewer; however, we feel it is important to list the devices that are FDA-approved, and the order in which they were FDA-approved. We also feel it is necessary to list the device names to be as clear as possible to the reader. We have declared no conflicts of interest and have no involvement with any of these companies. We are using the names of the products from the journals that we cited in this manuscript.

Thank you

Reviewer 4:

Dear Editor in Chief

My comments are as below:

Word count is unacceptable high! Reduce it to total about 6000 count. We had reduced the word count, but the reviewers have asked us to add in several sections of writing and have requested more detail, which we have provided in this revised version. We are trying to accommodate the reviewer's requests while also adding in the information they have requested.

Describe the methodology: We have added in a section that states: This was a narrative review. The sources for this review are as follows: Searching on PubMed, Google Scholar, Medline, and

ScienceDirect from 1990-2019 using keywords: Peripheral Neuromodulation, Headache, vagus nerve, occipital nerves, sphenopalatine ganglion.

Write discussion at the end of paper We have added a discussion that reads: **Discussion**

Neuromodulation is an expanding field of study for headache treatment aimed at noninvasive therapy to reduce pain by targeting structures within the nervous system commonly involved in headache pathophysiology, such as the vagus nerve (VNS) or sphenopalatine ganglion (SPG) for stimulation (9). The first noninvasive neurostimulator device approved for migraine treatment was the Cefaly device. The Cefaly device is an external trigeminal nerve stimulation device (e-TNS) that transcutaneously excites the supratrochlear and supraorbital branches of the ophthalmic nerve (V1) via a bipolar self-adhesive electrode (30 x 94 mm) applied to the forehead. Larger randomized-controlled trials (RCT) are necessary to fully define the versatility of Cefaly eTNS application in migraine treatment. The second noninvasive neurostimulation device receiving FDA approval was the single-pulse transcranial magnetic stimulator, SpringTMS (sTMS). Similar to the evidence for eTNS, more rigorous randomized controlled trials are needed to elucidate the efficacy across the heterogenous migraineur population and long-term safety of sTMS. GammaCore is a handheld transcutaneous vagal nerve stimulator applied directly to the neck at home by the patient for treatment of cluster headache (CH) and migraine. GammaCore is not as widely studied in migraine, however, initial results have proven promising.

Several other non-FDA-approved devices are in development to treat headache and target headache evolution at different levels and inputs. They require more research in different age populations to be considered as prescribed treatments. The Scion device is a caloric vestibular stimulator (CVS) used for 20 minutes once or twice a day. The device interfaces with the user

through a set of small cones resting in the ear canal on either side and held in place by modified over-ear headphones. The sphenopalatine ganglion (SPG) has long been a target for headache treatment. The pulsante SPG Microstimulator is a device implanted in the upper jaw via an hour-long oral procedure. And finally, the occipital nerve stimulator (ONS). The device consists of an implanted pulse generator on the chest wall connected to a subcutaneous lead with 4-8 electrodes that is tunneled the occiput.

Limitation? We have an entire section of the paper that is dedicated to limitations and have updated it to read: **Limitations of Therapy**

While there have been promising initial results from invasive and noninvasive neuromodulation devices for headache, there is still much about the mechanism that is unknown. Pending completion of further pilot trials, clinical trials in controlled settings are required for many of these devices to receive FDA approval for use in provider settings as an abortive or prophylactic treatment beyond refractory intervention. Transcranial magnetic stimulation has been FDA approved for use in patients with migraines with aura as abortive therapy and is now expanding for approval in chronic migraines (66). The upfront cost of interventional management is often offset in the long term with reduced use of pharmaceutical agents; however, most neuromodulatory procedures are indicated only in refractory cases (67). Several studies aimed at improving lead placement for ONS to reduce adverse events associated with lead migration post implantation; however, this specialized technique can serve as a barrier to the ability of providers to offer neuromodulation as a common therapy (68). Further ongoing studies on neuromodulation are investigating the specified targets and mechanisms of action of treatment. Much of this updated technology is new, and the long-term impact is not yet clear (71). Additional limitations include surgical error, adverse events, individualized patient response

to therapy, and patient user error.

Consider below three references: We have added these references to the paper

Zhou L, Ashkenazi A, Smith J W, Jen N, Deer TR, et al. Long-Term Clinical Outcome of Peripheral Nerve Stimulation for Chronic Headache and Complication Prevention. Anesth Pain Med. 2016;6(4):e35983.

Buture A, Gooriah R, Nimeri R, Ahmed F. Current Understanding on Pain Mechanism in Migraine and Cluster Headache. Anesth Pain Med. 2016;6(3):e35190.

Divizia M, Germani G, Urti I, Imani F, Varrassi G, et al. Endoscopic Neuromodulation of Suprascapular Nerve in Chronic Shoulder Pain: A Case Report. Anesth Pain Med. 2020;10(2):e103624.

Sincerely,



Dr. Elyse M. Cornett, PhD
Assistant Professor, Department of Anesthesiology
Director of Research, Department of Anesthesiology
Assistant Professor, Department of Pharmacology, Toxicology & Neuroscience
Assistant Professor of Research, Department of Anesthesiology, LSU New Orleans
LSU Health Shreveport
1501 Kings Highway
P.O. Box 33932
Shreveport, LA 71130-3932
c.248-515-9211
w.318-626-2348

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 17 Nov 2020

Dear AE,
Fortunately, the author has corrected the majority of the requested items. Therefore it can be considered for the next step in the publishing process.
Kind regards

REFEREE: Associate Editor | **Revision** (1) 17 Nov 2020

Dear EIC,
Based on reviewers' comments this revised format can be considered as Acceptance.
Sincerely yours

REFEREE: EIC | **Revision** (1) 17 Nov 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.