Cluster headache: expansion of the clinical spectrum

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Chapter 9

General discussion

The research presented in this thesis was aimed to investigate different parts of the cluster headache puzzle. The first aim was to develop and validate web-based diagnostic questionnaires to reliably recruit a large population of cluster headache patients for large scale genetic studies. Secondly, we wanted to study comorbid diseases and clinical features. The third aim was to assess the effect of occipital nerve stimulation, in medically intractable chronic cluster headache.

Part 1 Cluster headache genetics

The LUCA study- validation of web-based questionnaires

In **Chapter 2** we report on the development and validation of a diagnostic web-based cluster headache questionnaire for the recruitment of a large population for hypothesis free genetic research. We also provided a shorter questionnaire with similar sensitivity, specificity and positive predictive value with three questions which we named the 'QATCH' (Quick Ascertainment of Cluster Headache), which indicates that males with headache attacks of short duration and long headache-free intervals of months to years are very likely to have cluster headache. Our web-based, stepwise programme was shown to be a strong and semi-automatic way to be able to collect hundreds of cluster headache patients. The LUCA program is still recruiting cluster headache patients and up till now 1698 cluster headache patients have been recruited of whom 891 DNA samples have been collected. This sample size, however, is not enough for a genome wide association (GWA) study in cluster headache and therefore international collaboration is needed. GWA studies allow simultaneous testing of hundreds to thousands of common (that is with a frequency >5% in the general population) DNA markers in several thousand cases and controls in a hypothesis-free manner. Such large sample sizes are needed to correct for the large number of statistical tests performed.

Recently, a GWA study in 99 Italian patients with cluster headache and a control sample of 360 age-matched cigarette smoking healthy individuals was performed. In this clearly underpowered study no statistically significant association at the genome-wide threshold was found.(1) However, the authors describe a suggestive association ($p=9.1 \times 10^{-6}$) with a common variant of

the pituitary adenylate cyclase activating peptide (PACAP) receptor gene *(ADCYAP1R1)* and a missense variant in the membrane metalloendopeptidase (*MME)* gene ($P=2.5 \times 10^{-5}$). The products of both genes have an essential function in pain mechanisms.

Earlier candidate gene studies on the familial hemiplegic migraine type 1 (FHM1) gene CACNA1A(2, 3), the *MTHFR* gene 677C>T polymorphism (involved in vascular oxidative stress response)(4) and the *PER3* clock gene and cluster headache(5) all failed.

We failed to find any association of HCRTR2 SNP rs2653349 (6) unlike two of three small association studies and a meta-analyses.(7-10) In our subsequent meta-analysis including our LUCA population and the three earlier studies, however, we found a significant association of this variant with cluster headache susceptibility. This remained after excluding the first study (this study was an outlier because of a much larger effect and the only South-European study), though with smaller effect size (odds ratio from 0.69 to 0.80). We believe, however, that the results of our meta-analysis should be interpreted with caution, because of the possible large influence of underpowered studies. Low power does not only decrease the chance to detect a true effect, but also increases the chance that a significant finding from a small study is not a true effect.(11) We, therefore, concluded that there is still no robust evidence for a true association between HCRTR2 SNP rs2653349 and cluster headache.

Part 2 Cluster headache: comorbidity and clinical features

Studying comorbidity may lead to unravel parts of the pathophysiology of a disease and may improve treatment strategies. In large genetic studies, comorbidity and the existence of a certain phenotype can also play an important role, as it reduces genetic heterogeneity. For example, this strategy has been used in genetic studies in migraine with and without aura(12, 13), migraine and stroke(14) and migraine and coronary artery disease.(15) Cluster headache with aura or comorbid depression may have a different genetic profile. Our LUCA population of well-defined cluster headache patients (described in **Chapter 2**)

is one of the largest in the world and provides a unique database with validated diagnoses of cluster headache and additional information on clinical features and comorbidity to investigate clinical features and comorbidity.

Depression and cluster headache

In **Chapter 3** we investigated whether depression is a comorbid condition of cluster headache. In 462 participants with cluster headache (394 episodic and 67 chronic) the odds for lifetime depression were almost three times higher in cluster headache patients (43.9%) compared to 179 controls (15.8%) (OR 2.77, 95% CI 1.70-4.51), in particular in chronic cluster headache. We did not ask for suicidal tendency as we felt a subject too delicate and we feared it would affect the response rate.

There is extensive evidence of comorbidity between depression and migraine where it increases risk of chronification.(16) Common serotonergic and dopaminergic pathways may be involved. Depression is present in 5% to 85% of patients with pain (depending on study setting) and 65% of patients with depression experience one or more pain syndromes.(17) A longitudinal study has shown that depressive symptoms predict future episodes of low back pain, neck-shoulder pain and musculoskeletal symptoms. In addition, the presence of chronic pain affected the effect of treatment and diagnostic process of depression.(17) Dysregulation of serotonin and norepinephrine might contribute to the comorbidity of depression and pain syndromes including migraine and cluster headache. Drug therapies, however, targeting the serotonergic system are proven to be very effective in cluster headache, for example triptans and ergotamine, but are mostly acute treatments.(18)

Future studies on depression and cluster headache should focus on the possible longitudinal bidirectional relationship to investigate causality between cluster headache and depression.

Allodynia and cluster headache

In **Chapter 4** we describe the presence of allodynia in cluster headache suggestive for central sensitisation. A total of 218/606 (36%) of cluster headache patients had allodynia during attacks. Independent risk factors were female gender (OR 2.05, 95% CI 1.28-3.29), low age at onset (OR 0.98, 95% CI

0.96- 0.99), lifetime depression (OR 1.63; 95% CI 1.06-2.50), comorbid migraine (OR 1.96; 95% CI 1.02-3.79), and recent attacks (OR 1.80; 95% CI 1.13-2.86). We found no relation between allodynia and duration of attacks or chronic cluster headache.

Although allodynia is particularly expressed in neuropathic pain, it has also been described in nociceptive pain.(19) The classification of the International Association for the study of pain (IASP) (http://www.iasp-pain.org) divides chronic pain syndromes into neuropathic and nociceptive pain syndromes. Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system. Nociceptive pain is pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors. Nociceptive pain is divided into somatic and visceral nociceptive pain. Somatic pain is characterized as well localized, intermittent, or constant and described as aching, gnawing, throbbing, or cramping. Visceral pain is described as deep, squeezing, or colicky, and is commonly referred to cutaneous sites, which may be tender. Where to classify cluster headache within this distinction is difficult as the mechanism of pain in cluster headache is complex. In cluster headache the anatomical and functional intactness of pain pathways and the possible occurrence of sterile neurogenic inflammation points to nociceptive trigeminal pain, probably triggered by hypothalamic activation. (19) Some researchers classify cluster headache as a somatic pain and migraine as a visceral pain based on the clinical characteristics of the headache attacks. (20) The same researchers also hypothesized that involvement of relatively more descending inhibitory interneurons in somatic pain (cluster headache) compared to visceral pain (migraine) in the nociceptive dorsal horn neurons should lead to allodynia in migraine but not in cluster headache. Our findings, however, seems to contradict this hypothesis.

Allodynia may be treated with tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentinoids, opioids, cannabinoids, lamotrigine, mexiletine, lidocaine gel and botulinum toxin-A.(21) Presence of allodynia may predict good or poor therapy response depending on the condition and drug used.(21, 22) Therefore, we suggest to investigate whether presence of allodynia in cluster headache might predict treatment response.

Cluster-tic syndrome

In **Chapter 5** we investigated the co-occurrence and features of trigeminal neuralgia in cluster headache suggestive of the so called cluster-tic syndrome. In total 11/244 (4.5%) of the cluster headache patients had attacks fulfilling ICHD-II criteria for trigeminal neuralgia. Most patients had symptoms in the first branch of the trigeminal nerve and none in the third branch. Trigger factors were reported by a minority of patients, and most patients reported that the short attacks were timely related to the cluster headache attacks. In all cases trigeminal neuralgia was ipsilateral to the side of the cluster headache attacks. Although the non-cluster headache attacks in these patients fulfilled the ICHD-II criteria of trigeminal neuralgia, we do not believe in a shared underlying mechanism of cluster headache and trigeminal neuralgia. The ICHD-III criteria mention cluster-tic in a note; 'some patients have been described to have both cluster headache and trigeminal neuralgia', with the additive '*sometimes referred to as* cluster-tic syndrome'. Either such patients have two separate diseases or might have cluster headache with ultra-brief attacks. We, therefore deem it more preferable to make two separate headache diagnoses and describe the atypical features and treat accordingly. Since our study was published, two new case-reports of possible cluster-tic syndrome have been published.(23, 24) In the first case attacks of SUNCT/trigeminal neuralgia and to some extent also cluster headache improved after microvascular venous decompression of the trigeminal nerve.(23) In the second case there was co-occurrence of trigeminal neuralgia with trigger points within the mandibular branch.(24) Attacks of cluster headache, but not of trigeminal neuralgia, responded well to non-invasive vagus nerve stimulation (VNS).(24) VNS is a promising new treatment for episodic but not chronic cluster headache.(25, 26) Whether VNS is also effective in trigeminal neuralgia, is unknown.

Cluster headache and aura

In **Chapter 6** we show that 22/244 (9.0%) cluster headache patients had (primarily visual) aura-symptoms preceding cluster headache attacks, which is lower than in other studies(27-29). The majority (72.7%) of these patients did not report comorbid migraine headache attacks.

In migraine, auras are thought to be caused by cortical spreading depolarisation possibly secondary to cortical hyperexcitability. Our findings suggest that both phenomena might also play a role in cluster headache with aura.

Cluster headache and epilepsy

In **Chapter 7** we show that epilepsy is more prevalent among cluster headache (2.0% (95% CI: 1.1, 3.4)) compared to the general population (0.76% (95% CI: 0.617, 0.938)).(30) Our results seem valid as we found the same increased prevalence of epilepsy in our migraine cohort as described in the literature of 0.7-2.3%.(31)

This finding supports the notion that cortical hyperexcitability might also be present as suggested by the increased prevalence of aura (**Chapter 6**) and cortical hyperexcitability after transcranial magnetic stimulation in episodic cluster headache.(32)

Part 3 The ICON study

In **Chapter 8** we describe the protocol for the ICON study which assesses the effect of occipital nerve stimulation in medically intractable chronic cluster headache patients. The ICON study is a prospective, randomised, double blind, sham controlled parallel group study. As participants might be unblinded by experiencing paraesthesia in an active versus inactive group, the ICON study compares a presumably therapeutically high (100%) versus a presumably low (30%) amplitude occipital nerve stimulation. To further mask the difference between high and low stimulation, the stimulation percentages were increased in a step-wise fashion over a period of 4 months. Primary outcome is the mean difference in the number of attacks over the last 4 weeks of the blinded study period of 6 months. After this blinded study period there will be an open extension phase of 6 months. Various secondary outcome measures are assessed as well including economic evaluation. To detect a 35% therapeutic gain versus placebo, 120 patients need to complete the 6 month placebo controlled double blind phase with 90% power and alpha of 0.05. Assuming a dropout rate of 20% we intended to randomise in total 144 patients. The first patient was included in October 2009 and was randomised in January 2010. At present, the trial is completed with 131 patients randomised, as the actual dropout rate was much lower than anticipated. Results are expected in the summer of 2019.

An incidental finding of our ICON study was that occipital nerve stimulation seems to be a safe and effective treatment during pregnancy.(33)

Future perspectives

Genetic research in cluster headache is still in its infancy. Epigenetics(34) involves several mechanisms (i.e. histone modifications, DNA methylation and non-coding RNAs) that regulate gene expression without changing the genetic code. Although there is a clear genetic component in cluster headache, environmental factors are likely to play a role as well. For example, epigenetics could be one of the mechanisms through which aging and environmental factors like smoking may exert their (long-lasting) effect on gene regulation in cluster headache.(35)

Another example is gene expression profiling, which can be studied in relatively small numbers of patients, clearly a benefit in a rare disease such as cluster headache. Gene expression profiling provides identification of genes and pathways resulting from genetic and epigenetic factors. A recent small study in 39 cluster headache patients and 20 controls showed only modest gene expression differences.(36) Additional tests suggested involvement of brain-related molecules (e.g. GABA and ion channels) and inflammation-related molecules. Using the same method the hypocretin gene sets were also tested because of previous findings of a relation between the *HCRTR2 gene* and cluster headache. No association was, however, found which is in accordance with our study results.(6) In the future, larger samples (n=100-120) are required to identify the full range of cluster headache related pathways and genes.

Finally, exome sequencing (sequencing all coding variants of an individual) might provide useful information assuming that a limited number of rare variants with high individual effect size underlie susceptibility to cluster headache. Results of exome sequencing in familial cluster headache cases are more likely to uncover parts of the pathophysiological mechanism, than studying the genetic profile of sporadic cases.

We believe that hypothesis-driven and underpowered studies are likely to provide invalid results and will not unravel the genetic pathophysiology of cluster headache.(6) So, other non-hypothesis driven strategies in large study cohorts (> 1000 patients) and replication cohorts are needed. With recruiting and validating our LUCA program we made the first step, but as international collaboration is needed to recruit sufficiently large cohorts, at this moment the first international collaboration for GWA studies in cluster headache is being established. In migraine, unfortunately until now GWA studies did not live up to the expectation of being able to predict individual risk to disease. It is likely that GWA studies in cluster headache will possibly also only identify gene variants with low relative risk and explain only a small proportion of disease heritability. Thousands of patients are needed to have enough power to detect associated SNP's which is challenging in a relatively rare disease as cluster headache.(12, 13) Moreover, interpretation of the associated SNP is often difficult, as GWA study hits are often located outside coding regions, which makes it hard to assess which genes are involved in the disease.

Calcitonin Gene-related peptide (CGRP) is increased in the external jugular vein blood in cluster headache during attacks and a normalization of CGRP occurred after spontaneous resolution or treatment with sumatriptan or O2.(37) This suggests a role of CGRP in the pathophysiology of cluster headache. CGRP is a potent vasodilator and has a prominent role in the transmission of pain.(38) In the trigeminal ganglion there is high expression of CGRP receptors. In migraine, phase II studies with small molecule CGRP receptor antagonists or monoclonal antibodies against CGRP or its receptor have shown promising results.(39-43) Trials in cluster headache on galcanezumab and fremanezumab are underway.

Promising neuromodulation therapies other than ONS are sphenopalatine ganglion (SPG) and VNS. In SPG stimulation an implantable microstimulator is fixed to the maxilla, with electrodes placed in the pterygopalatine fossa proximate to the SPG. The device offers acute efficacy for attacks.(44) There was also some prophylactic effect, but this needs to be confirmed in larger dedicated studies.(45)
One of the disadvantages of the prescribed invasive neuromodulation studies is the relatively high number of hardware failure and complications (lead migrations in 30% and infection in 3-5%) and the need for surgery. This led to

the development of a non-invasive technique: non-invasive VNS. In the past, invasive VNS has been used for the treatment of epilepsy and medication resistant depression and also showed promising results in cluster headache.(46) More recently, a new device for non-invasive VNS was developed. A randomised, not blinded trial showed a significant weekly attack frequency reduction using daily prophylactic non-invasive VNS as an adjunctive to standard of care as compared to standard of care alone (p=0.02).(47) Subsequently a randomised, double blind sham controlled study showed that non-invasive VNS was effective in episodic but not in chronic cluster headache.(25, 48) The device was safe and well tolerated.

References

1. Bacchelli E, Cainazzo MM, Cameli C, Guerzoni S, Martinelli A, Zoli M, et al. A genome-wide analysis in cluster headache points to neprilysin and PACAP receptor gene variants. J Headache Pain. 2016;17(1):114.
2. Haan J, Vliet JAv, Kors EE, Terwindt GM, Vermeulen FL, Maagdenberg AMvd, et al. No involvement of the calcium channel gene (CACNA1A) in a family with cluster headache. Cephalalgia. 2001;21(10):959-62.
3. Sjöstrand C, Giedratis V, Ekbom K, Waldenlind E. CACNA1A gene polymorphisms in cluster headache. Cephalalgia. 2001;21:953-8.
4. Schurks M. Genetics of cluster headache. CurrPain Headache Rep. 2010;14(2):132-9.
5. Ofte HK, von Hanno T, Alstadhaug KB. Retinal vasculature in cluster headache. Cephalalgia. 2016.
6. Weller CM, Wilbrink LA, Houwing-Duistermaat JJ, Koelewijn SC, Vijfhuizen LS, Haan J, et al. Cluster headache and the hypocretin receptor 2 reconsidered: A genetic association study and meta-analysis. Cephalalgia. 2014.
7. Rainero I, Gallone S, Rubino E, Valfre W, Vaula G, Pinessi L. Association between polymorphisms and haplotypes of the HCRTR2 gene and cluster headache. Neurology. 2007;68(12):A306-A.
8. Rainero I, Gallone S, Valfre W, Ferrero M, Angilella G, Rivoiro C, et al. A polymorphism of the hypocretin receptor 2 gene is associated with cluster headache. Neurology. 2004;63(7):1286-8.
9. Schurks M, Kurth T, Geissler I, Tessmann G, Diener HC, Rosskopf D. Cluster headache is associated with the G1246A polymorphism in the hypocretin receptor 2 gene. Neurology. 2006;66(12):1917-9.
10. Baumber L, Sjostrand C, Leone M, Harty H, Bussone G, Hillert J, et al. A genome-wide scan and HCRTR2 candidate gene analysis in a European cluster headache cohort. Neurology. 2006;66(12):1888-93.
11. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14(5):365-76.
12. Freilinger T, Anttila V, de VB, Malik R, Kallela M, Terwindt GM, et al. Genome-wide association analysis identifies susceptibility loci for migraine without aura. NatGenet. 2012;44(7):777-82.
13. Anttila V, Stefansson H, Kallela M, Todt U, Terwindt GM, Calafato MS, et al. Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. NatGenet. 2010;42(10):869-73.
14. Malik R, Freilinger T, Winsvold BS, Anttila V, Vander Heiden J, Traylor M, et al. Shared genetic basis for migraine and ischemic stroke: A genome-wide analysis of common variants. Neurology. 2015;84(21):2132-45.
15. Winsvold BS, Nelson CP, Malik R, Gormley P, Anttila V, Vander Heiden J, et al. Genetic analysis for a shared biological basis between migraine and coronary artery disease. Neurol Genet. 2015;1(1):e10.
16. Louter MA, Bosker JE, van Oosterhout WP, van Zwet EW, Zitman FG, Ferrari MD, et al. Cutaneous allodynia as a predictor of migraine chronification. Brain. 2013;136(Pt 11):3489-96.
17. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med. 2003;163(20):2433-45.
18. Lambru G, Matharu M. Serotonergic agents in the management of cluster headache. Curr Pain Headache Rep. 2011;15(2):108-17.
19. de Tommaso M, Vecchio E. Primary headaches and trigeminal neuralgia: neuropathic pain yes or not? Evidences from neurophysiological procedures. Expert Rev Neurother. 2013;13(9):1031-9.
20. Burstein R. Should cluster headache be associated with cutaneous allodynia? Cephalalgia. 2006;26(9):1041-2.
21. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. Lancet Neurol. 2014;13(9):924-35.
22. van Eijs F, Smits H, Geurts JW, Kessels AG, Kemler MA, van Kleef M, et al. Brush-evoked allodynia predicts outcome of spinal cord stimulation in complex regional pain syndrome type 1. Eur J Pain. 2010;14(2):164-9.

23. de Coo I, van Dijk JM, Metzemaekers JD, Haan J. A Case Report About Cluster-Tic Syndrome Due to Venous Compression of the Trigeminal Nerve. Headache. 2016.
24. Kinfe TM, Pintea B, Guresir E, Vatter H. Partial Response of Intractable Cluster-Tic Syndrome Treated by Cervical Non-Invasive Vagal Nerve Stimulation (nVNS). Brain Stimul. 2015;8(3):669-71.
25. Goadsby PJ, de Coo IF, Silver N, Tyagi A, Ahmed F, Gaul C, et al. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A randomized, double-blind, sham-controlled ACT2 study. Cephalalgia. 2018;38(5):959-69.
26. Holle-Lee D, Gaul C. Noninvasive vagus nerve stimulation in the management of cluster headache: clinical evidence and practical experience. Ther Adv Neurol Disord. 2016;9(3):230-4.
27. Bahra A, May A, Goadsby PJ. Cluster headache. A prospective clinical study with diagnostic implications. Neurology. 2002;58:354-61.
28. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. Headache. 2012;52(1):99-113.
29. Evans RW, Krymchantowski AV. Cluster and other nonmigraine primary headaches with aura. Headache. 2011;51(4):604-8.
30. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology. 2017;88(3):296-303.
31. Keezer MR, Bauer PR, Ferrari MD, Sander JW. The comorbid relationship between migraine and epilepsy: a systematic review and meta-analysis. EurJNeurol. 2014.
32. Cosentino G, Brighina F, Brancato S, Valentino F, Indovino S, Fierro B. Transcranial magnetic stimulation reveals cortical hyperexcitability in episodic cluster headache. JPain. 2015;16(1):53-9.
33. de Coo IF, Wilbrink LA, Haan J. Effective occipital nerve stimulation during pregnancy in a cluster headache patient. Cephalalgia. 2016;36(1):98-9.
34. Eising E, N AD, van den Maagdenberg AM, Ferrari MD. Epigenetic mechanisms in migraine: a promising avenue? BMC Med. 2013;11:26.
35. Schurks M, Kurth T, de JJ, Jonjic M, Rosskopf D, Diener HC. Cluster headache: clinical presentation, lifestyle features, and medical treatment. Headache. 2006;46(8):1246-54.
36. Eising E, Pelzer N, Vijfhuizen LS, Vries B, Ferrari MD, t Hoen PA, et al. Identifying a gene expression signature of cluster headache in blood. Sci Rep. 2017;7:40218.
37. Tfelt Hansen PL, Han. Calcitonin gene-related peptide in blood: is it increased in the external jugular vein during migraine and cluster headache? A review. The Journal of Headache and Pain. 2009;10(3):137-43.
38. Arulmani U, Maassenvandenbrink A, Villalon CM, Saxena PR. Calcitonin gene-related peptide and its role in migraine pathophysiology. Eur J Pharmacol. 2004;500(1-3):315-30.
39. Ho TW, Connor KM, Zhang Y, Pearlman E, Koppenhaver J, Fan X, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology. 2014;83(11):958-66.
40. Recober A, Russo AF. Olcegepant, a non-peptide CGRP1 antagonist for migraine treatment. IDrugs. 2007;10(8):566-74.
41. Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol. 2016;15(4):382-90.
42. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings EL, Diener HC, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015;14(11):1091-100.
43. Tepper S, Ashina M, Reuter U, Brandes JL, Dolezil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(6):425-34.
44. Schoenen J, Jensen RH, Lanteri-Minet M, Lainez MJ, Gaul C, Goodman AM, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. Cephalalgia. 2013;33(10):816-30.

45. Barloese MC, Jurgens TP, May A, Lainez JM, Schoenen J, Gaul C, et al. Cluster headache attack remission with sphenopalatine ganglion stimulation: experiences in chronic cluster headache patients through 24 months. J Headache Pain. 2016;17(1):67.
46. Mauskop A. Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. Cephalalgia. 2005;25(2):82-6.
47. Gaul C, Diener HC, Silver N, Magis D, Reuter U, Andersson A, et al. Non-invasive vagus nerve stimulation for PREVention and Acute treatment of chronic cluster headache (PREVA): A randomised controlled study. Cephalalgia. 2016;36(6):534-46.
48. Silberstein SD, Mechtler LL, Kudrow DB, Calhoun AH, McClure C, Saper JR, et al. Non-Invasive Vagus Nerve Stimulation for the ACute Treatment of Cluster Headache: Findings From the Randomized, Double-Blind, Sham-Controlled ACT1 Study. Headache. 2016;56(8):1317-32.