Authors (Ref)	Stimulation protocol	Primary outcomes	Secondary outcomes	Conclusion
Goadsby et al. (2014) *(38)*	1) treat up to four acute migraine attacks within six weeks 2) treatment consisted of two, 90s doses, at 15 minute intervals delivered to the right cervical branch of the vagus nerve. 3) subjects were asked to self-treat once pain became moderate or severe, or after 20 minutes of mild pain	21% of patients pain-free at 2h for the first treated attacks	22% Pain-free at 2h	nVNS may be an effective and well-tolerated treatment method in patients with acute migraine.
Kinfe et al. (2015) *(39)*	1) for prophylactic therapy, patients were instructed to administer one 2 minutes stimulation of nVNS to the cervical branch of the vagus nerve on each side of the neck, twice daily (morning and late afternoon; total of 4 doses per day) 3) for acute therapy, patients were advised to administer one 2 minutes stimulation of nVNS to the cervical branch of the vagus nerve on each side of the neck at the time of acute medication intake	Significant reduction in median VAS-scores ($p<0.001$) post-treatment	Significant reduction in number of headache days: attacks per month ($p<0.001$)	A clinically meaningful response to prophylactic use of nVNS therapy was observed. Large randomized, sham-controlled trials are needed.
Barbanti et al. (2015) *(40)*	1) patients were instructed to use nVNS to self-treat up to three consecutive migraine attacks that occurred over a 2-week period. 2) for each migraine attack, patients delivered two 120 seconds doses of electrical stimulation at 3 minute intervals to the right cervical branch of the vagus nerve within 20 min of the onset of mild or moderate pain. 3) patients were allowed to take a rescue medication if they perceived no reduction in pain 2 hours after nVNS treatment.	56.3% of patients reported pain-relief at 1h and 64.6% at 2h post-treatment	35.4% and 39.6% of patients pain-free at 1h and 2h, respectively.	nVNS may be an effective acute treatment for high-frequency episodic or chronic migraine. Furthermore, it helps to reduce medication overuse and adverse events associated with medication.
Grazzi et al (2015) *(42)*	1) patients treated 3-5 migraine attacks in 3 weeks with nVNS 2) treatment consisted of one, 90 seconds dose delivered to the right cervical branch of the vagus nerve. 3) subjects were asked to treat attack from moderate to severe and also to record on a visual analogue scale the level of pain in an interval of time from 30 min to 24 h after the device application.	39.2% of attacks resolved completely within 30min.	44.6% of attacks nVNS didn't show any beneficial effects in the first 2h.	The study reports good efficacy of nVNS in the management of migraine attacks
Silberstein et al. (2016) *(43)*	1) stimulations delivered 5–10 minutes apart to the right side of the neck at 3 pre-specified times every day: (1) within 1 hour of awakening; (2) 6–8 hours after the first treatment; and (3) 6–8 hours after the second treatment	No significant differences between number of headache days or tolerability between active and sham ($p=0.56$).	Significant greater reduction in headache days in active treatment group after the open-label phase ($p<0.01$).	nVNS was non-harmful and well-tolerated. Prophylactic use may reduce the number of headache days in chronic migraine. Larger randomized, sham-controlled studies are needed.
Grazzi et al (2017) *(22)*	1) over a 4-week period (4 to 8 episodes), patients delivered one session of 120 seconds of electrical stimulation on the right side of the neck 2) a second stimulation was allowed within 1 hour of the first stimulation as needed, if the patient was not pain free.	Acute treatment effective in 46.8% of migraine attacks	No rescue medication was required	nVNS is safe and well-tolerated and practical for the treatment of migraine. Study provides a rationale for larger randomized studies.
Tassorelli et al (2018)* *(41)*	1)within 20 minutes from migraine pain onset, participants self-administered bilateral 120-second stimulations to the right and left sides of the neck	Significantly higher proportion of subjects pain-free at 30 minutes and 60 minutes after the first treated attack ($p=0.023$)	Significantly higher responder rates for pain relief at 120 minutes the first treated attack ($p=0.030$)	The trial supports the abortive efficacy of nVNS. Furthermore, the findings suggest effective pain relief, tolerability, and practicality of nVNS for acutely treating episodic migraine

Nesbitt et al. (2015) *(44)*	1) patients administered up to 3 consecutive doses to treat an attack acutely. 2) for preventive use, they administered 2 (and in some cases 3) consecutive doses in the morning and late afternoon (approximately 8 hours apart) daily. 3) either form of stimulation was delivered on the side of the neck ipsilateral to the majority of their cluster attacks.	Mean overall estimated improvement of 48%	Almost half of the attacks was aborted within ~11min after stimulation.	nVNS may be effective and practical in the treatment of chronic cluster headache, acutely and preventive.
Gaul et al. (2016) *(45)*	1) mandatory nVNS prophylaxis consisted of three 2-minute stimulations (i.e. three doses) five minutes apart administered twice daily (i.e. six doses per day) to the right side of the neck (right vagal nerve). 2) first prophylactic treatment was administered within one hour of waking 3) the second was administered seven to 10 hours after the first treatment 4) number, duration, frequency, and timing of doses were chosen according to previously reported nVNS dosing parameters 5) participants also had the option of acutely treating CH attacks with three additional nVNS doses at pain onset but were advised to not administer prophylactic therapy within a two-hour period after acute treatment	Significant reduction in weekly attack frequency compared to controls: mean therapeutic gain: 3.9 (p=0.02)	Higher ≥50% response rates observed within active treatment group.	The clinical relevance of nVNS in patients with chronic migraine is demonstrated. It helps to reduce attack frequency, offering clinical benefits beyond patients treated with sham
Silberstein et al. (2016) *(46)*	1) subjects administered three consecutive 2-minute stimulations to the right side of the neck at the onset of premonitory symptoms or pain. 2)subjects self-treated up to five cluster headache attacks in the double-blind phase 3) only one attack could be treated during a 12-hour period. 4) no limitations on the number of attacks that could be treated in the open-label phase	Higher response rate in active treatment group than controls (p=0.1)	Significantly higher response rates in nVNS group for eCH cohort, but not for cCH cohort (p=0.008)	nVNS is safe and well-tolerated and opens new doors in the acute treatment of cluster headache
Goadsby et al. (2017) *(23)*	1) subjects were instructed to self-administer three consecutive 120-seconds of stimulations ipsilateral to their cluster headache attack at the time of attack onset 2) if the attack was not aborted within nine minutes after initiation of the first stimulation, three additional consecutive stimulations were allowed during a treatment session, in order to have an endpoint measurement at 15 minutes 3) a minimum of six hours was required between treatment sessions	No significant difference in pain-free rates between nVNS and sham in for total cohort (p=0.71)	Significantly higher pain-free rates with nVNS than with sham in eCH subgroup. No treatment difference seen in cCH subgroup (p=0.13)	The results indicate that nVNS is safe and effective in the treatment of eCH. However, the data doesn't support the use of nVNS in cCH.
Trimboli et al. (2017) *(21)*	1) subjects were instructed to apply two consecutive nVNS doses (90 seconds each) on one side of the neck or alternating right and left sides, three times a day, as a preventive stimulation paradigm. 2) as an acute treatment for headache episodes, patients were advised to use up to three additional consecutive doses before resorting to their usual abortive treatment	87% chronic migraine patients, 8.3% cCH and 50% of patients with HC responded to nVNS treatment.	None of SUNA patients benefited from nVNS therapy	The results suggests that nVNS may not be a meaningful preventive nor acute treatment option in the treatment of patients with primary refractory headache disorders. However, the use of nVNS in HC patients may constitute an effective preventive option. Further exploration in larger studies is being warranted.
Tso et al (2017) *(47)*	not provided	78% Of patients with HC reported reduced severity of continuous pain	67% of patients with PH reported beneficial effects from nVNS	This initial experience suggests a beneficial role of nVNS in patients with indomethacin-sensitive TACs

Supporting Table 2: Overview of characteristics of the included nVNS studies in primary headache disorders and their subjects: part 2

cCH: Chronic Cluster Headache; eCH: Episodic Cluster Headache; HC: Hemicrania Continua; nVNS: Non-invasive Vagus Nerve Stimulation; PH: Paroxysmal Hemicrania; SUNA: Short-lasting Unilateral Neuralgiform headache Attacks with cranial Autonomic features; VAS: Visual Analogue Scale; *: Intention to treat data