Therapeutic strategies that act on the peripheral nervous system in primary headache disorders

János Tajti, Délia Szok, Aliz Nyári & László Vécsei

Submit your article to this journal

Article views: 151

View Crossmark data

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS | Check for updates

Therapeutic strategies that act on the peripheral nervous system in primary headache disorders

János Tajti[a], Délia Szok[a], Aliz Nyári[a] and László Vécsei[a,b]

[a]Department of Neurology, Faculty of Medicine, Interdisciplinary Excellence Centre, University of Szeged, Szeged, Hungary; [b]MTA-SZTE Neuroscience Research Group of the Hungarian Academy of Sciences, Szeged, Hungary

ABSTRACT

Introduction: Acute and preventive treatment of primary headache disorders is not completely resolved with regard to efficacy, safety, and tolerability. Hence, peripheral and central neuromodulation can provide therapeutic alternatives in drug-resistant cases. Peripheral targets of neuromodulation include invasive and non-invasive neurostimulation and electrical and chemical nerve and ganglion blockades.

Areas covered: A PubMed search of papers published from January 2012 to October 2018 was conducted. The goal of this review was to analyze the efficacy and safety of invasive (implantable) peripheral neurostimulation methods (the occipital nerve, the cervical branch of vagal nerve, the sphenopalatine ganglion) and non-invasive (transcutaneous) peripheral neurostimulation methods (the occipital nerve, the supraorbital nerve, and the cervical and auricular branches of the vagal nerve), based on the results of published clinical trials and case series. Acting also on the peripheral nervous system, peripheral nerve (i.e. greater occipital nerve) and ganglion (i.e. sphenopalatine ganglion) blockades, botulinum neurotoxin type A-hemagglutinin complex therapies, and calcitonin gene-related peptide-related monoclonal antibody treatments in this patient population are also discussed.

Expert opinion: This review summarizes the latest results on the therapeutic strategies acting on the periphery in primary headache disorders. These therapeutic options are minimally invasive or non-invasive, efficacious, safe, and well tolerated.

1. Introduction

Treating drug-resistant (a.k.a. refractory) primary headache patients represents a big challenge at different levels of health care from the emergency department setting to the tertiary headache center. By consensus, the definition of refractory is that patients do not respond to the current and adequate medications [1]. In this special patient population, some potential peripheral nervous system therapeutic options are available. The rationale for these different methods is not fully elucidated, but they are predominantly connected with the leading hypothesis of the activation and sensitization of the trigeminovascular system.

Peripheral neuromodulatory techniques include neurostimulation methods and peripheral nerve or ganglion blockades. Peripheral neurostimulation in primary headache disorders can be divided into non-invasive (i.e. transcutaneous) and invasive (i.e. surgically implanted) methods. Non-invasive methods are: transcutaneous occipital nerve stimulation (ONS), transcutaneous supraorbital nerve stimulation (SONS; the Cefaly® device), transcutaneous cervical vagal nerve stimulation (VNS; the gammaCore® device), and transcutaneous auricular VNS (the NEMOS® device) [2,3]. Invasive neurostimulation techniques include the following: implantable ONS, implantable SONS, implantable cervical VNS, and implantable sphenopalatine ganglion (SPG) stimulation (the Pulsante SPG Microstimulator System®). In pharmacoresistant

migraine and trigeminal autonomic cephalalgias (TACs), both non-invasive and invasive peripheral neurostimulation techniques are indicated either as abortive (a.k.a. acute) or prophylactic (a.k.a. preventive) treatment [1]. In intractable migraine and cluster headache (CH), nerve and ganglion blockades, as minimally invasive procedures using chemical agents or radiofrequency (RF) ablation are recommended. Furthermore, in drug-refractory episodic (EM) or chronic migraine (CM), botulinum neurotoxin type A (BoNTA)-hemagglutinin complex injection and the novel parenteral calcitonin gene-related peptide (CGRP)-related monoclonal antibody (mAb) treatment are also applicable.

The aim of this review is to provide a comprehensive summary of the current status of peripheral nervous system-targeted therapeutic strategies in patients with refractory primary headache disorders.

2. Methods

Papers selected for this work were searched within the PubMed database by using the keywords 'headache', 'primary headache disorders', 'migraine', 'tension-type headache', 'trigeminal autonomic cephalalgias', 'CGRP monoclonal antibody', 'cluster headache', 'SUNCT', 'SUNA', 'SUNHA', 'hemicrania continua', 'neurostimulation', 'nerve blockade', 'occipital nerve stimulation', 'vagal nerve stimulation', 'supraorbital nerve stimulation',

---

'sphenopalatine ganglion stimulation', and/or 'botulinumtoxin'. Only abstracts published in English were considered. The literature search was conducted in October 2018. The earliest date of publication considered was January 2012, except for 'botulinumtoxin', where the search included studies from 2010. The authors overviewed clinical trials of various levels, as well as case series, and classified and ranked the data based on the design of the research. All authors contributed to the literature review.

3. Migraine

Migraine is a common neurovascular disorder with high socioeconomic impact. The two forms of EM are migraine without and with aura. CM is a subclass of migraine with a prevalence of 8% among migraineurs and about 2% of the general population [4]. It highly influences the quality of life of the patients, because these sufferers have at least 15 headache days per month (8 out of 15 days with migraine with or without aura) for at least three consecutive months [5].

3.1. Neurostimulation in migraine

3.1.1. Non-invasive (i.e. transcutaneous) neurostimulation in migraine
3.1.1.1. Transcutaneous ONS in migraine.
There is at present insufficient data for the usefulness of transcutaneous ONS in drug-refractory migraine [6] and only a few studies have so far been published (Tables 1 and 2(a)).
3.1.1.1.1. Randomized controlled trials (RCTs) of transcutaneous ONS in EM.
A prospective RCT for EM prevention (n = 110) using transcutaneous ONS at different frequencies (2 Hz, 10 Hz, and 2/100 Hz) showed a higher 50% responder rate in each test group compared to the sham group, without any serious adverse events (AEs) [7].
3.1.1.1.2. Single-center studies of transcutaneous ONS in mixed headache.
A single-center, open-label study of transcutaneous ONS in 41 drug-resistant headache patients (including patients with occipital neuralgia, cervicogenic headache, CH, and CM) revealed that the mean Visual Analogue Scale (VAS) pain score decreased from 5.9 (at baseline) to 2.2 (after transcutaneous ONS treatment). The response to ONS was better in the case of good or excellent preoperative response to transcutaneous electrical nerve stimulation (TENS) compared to those with only moderate preoperative response to TENS [8].

Table 1. Peripheral neurostimulation methods in drug-resistant primary headache disorders.

Invasive		Non-invasive	
Method	Indications	Method	Indications
Implantable ONS	Intractable chronic migraine Intractable chronic cluster headache Intractable SUNCT and SUNA Intractable hemicrania continua	Transcutaneous ONS	Drug-refractory episodic migraine Drug-refractory custer headache
Implantable SONS+ONS	Intractable chronic migraine	Transcutaneous SONS (The Cefaly® device)	Drug-refractory episodic migraine
Implantable cervical branch VNS	Epileptic patients with headache	Transcutaneous cervical VNS (the gammaCore® device) Transcutaneous auricular VNS (the NEMOS® device)	Drug-refractory episodic and chronic migraine Drug-refractory episodic and chronic cluster headache Drug-refractory SUNA Drug-refractory hemicrania continua Drug-refractory chronic migraine
Implantable SPG stimulation (The Pulsante SPG Microstimulator System®)	Intractable episodic and chronic cluster headache		

Abbreviations: ONS = occipital nerve stimulation; SONS = supraorbital nerve stimulation; SPG = sphenopalatine ganglion; SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; VNS = vagal nerve stimulation.

Table 2A. Data of the occipital nerve neurostimulation (ONS) studies in drug-refractory primary headache disorders.

Study design	Migraine		Cluster headache (CH)		Other TACs	
	Episodic migraine (EM)	Chronic migraine (CM)	Episodic CH	Chronic CH	SUNHA	Hemicrania continua
Non-invasive (transcutaneous) occipital nerve stimulation (ONS)						
RCT (for prevention) (2017) [7]	n = 110 E = 40.91% (at 100 Hz) versus 4.55% (sham) AEs = no serious AEs					
Invasive (implantable) occipital nerve stimulation (ONS)						
RCT (long-term) (2015) [46]		n = 125 (intractable CM) E: headache days reduced by 7.7 (±8.7) days AEs: lead migration, persistent pain, and/or numbness				
RCT (2015) [47]		n = 15 E: suprathreshold vs. subthreshold stimulation (1.98 ± 1.56 vs. 5.65 ± 2.11) AEs: none				
RCT (2012) [48]		n = 157 E: failed AEs: persistant implant side pain, lead migration				
Prospective RCT (the ICON study) **(2013)** [115]				ongoing		
Open-label prospective long-term uncontrolled observational **(2017)** [49]		n = 37 E: VAS decreased by 4.9 ± 2.0 AEs: none				
Open-label prospective cohort (2018) [50]		n = 35 E: 28,5% of the patients AEs: not mentioned				
Open-label prospective cohort (2018) [50]				n = 33 E: 54.5% of the patients AEs: not mentioned		
Open-label monocentric long-term (2017) [117]				n = 35 E: 66.7% of the patients AEs: battery depletion, electrode migration		
Open-label long-term prospective **(2013)** [143]					n = 9 E: 8 out of 9 of the patients AEs: lead migration, muscle pain	
Open-label long-term follow-up prospective (2017) [144]						n = 16 E: 75% of the patients AEs: none
Cross-over prospective randomized (2012) [51]		n = 30 E: 54–60% of patients AEs: infection, lead migration				
Single-center combined ONS and SONS (2013) [52]		n = 14 E: 71% of patients AEs: lead migration				

(Continued)

Table 2A. (Continued).

Study design	Migraine		Cluster headache (CH)		Other TACs	
	Episodic migraine (EM)	Chronic migraine (CM)	Episodic CH	Chronic CH	SUNHA	Hemicrania continua
Long-term functional outcome combined ONS and SONS (2016) [53]		n = 16 E: 50% of patients AEs: lead migration, supraorbital lead allodynia, infection				
Long-term retrospective (2013) [54]		n = 25 E: 53% of patients AEs: lead displacement, local infection				
Single-center observational (2014) [55]		n = 17 E: NRS = 9.8 + 0.7 (at baseline), 5.0 ± 1.6 (at 3 months); 5.7 ± 2.6 (at 12 months) AEs: lead migration				
Single-center prospective long-term (2013) [118]				n = 24 E: 89% of the patients AEs: local pain, local infections		
Single-center long-term follow-up (2017) [119]				n = 16 E: 75% of the patients AEs = electrode migration, battery replacement, infection		
Observational prospective (2017) [120]				n = 67 E: 59% of the patients AEs: early battery depletion		
Literature review (2017) [149]					n = 7 E: 100% of the patient AEs: none	

Abbreviations: AE = adverse event; CH = cluster headache; E = effectiveness (at least 50% improvement in headache frequency and/or intensity); GON = greater occipital nerve; n = number of the randomized patients; NRS = numeric rating scale; RCT = randomized multicenter double-blind controlled trial; SON = supraorbital nerve; SUNHA = short-lasting unilateral neuralgiform headache attacks; TAC = trigeminal autonomic cephalalgia; VAS = Visual Analogue Scale.

Table 2B. Data of the greater occipital nerve (GON) blockade studies in intractable primary headache disorders.

Study design	Migraine		Cluster headache (CH)		Other TACs	
	Episodic migraine (EM)	Chronic migraine (CM)	Episodic CH	Chronic CH	SUNHA	Hemicrania continua
	Greater occipital nerve (GON) blockade with chemical agents					
RCT (bupivacaine) (2017) [58]		n = 44 E = frequency: 21.0 (at baseline) versus 6.3 (at 3 month); intensity: 8.9 (at baseline) versus 6.3 (at 3 month) AE = local pain, vertigo, nausea				
RCT (bupivacaine) (2017) [59]		n = 36 E = number of headache days: 4.9 (pretreatment) to 3.4 (post-treatment) AE = stinging sensation, presyncope				
RCT prospective pilot (bupivacaine) (2015) [60]		n = 23 E = pain intensity: VAS: 3.93 (pre-injection) versus VAS: 1.55 (post-injection) AE = no serious AE				
RCT (bupivacaine) (2015) [61]		n = 84 E = headache days: from 18.1 (at baseline) to 8.8 (at 1 month); VAS = from 8.4 (at baseline) to 5.3 (at 1 month) AEs = local pain, vertigo				
RCT (bupivacaine plus methylprenisolone) (2015) [64]	n = 70 E = 30% of the active and placebo groups AEs = pain at injection side					
RCT (lidocaine plus saline versus lidocaine plus triamcinolone) (2014) [65]	n = 48 E = pain intensity: 5.46 (lidocaine plus triamcinolone group) versus 5.29 (lidocaine plus saline group) at week 8; headache frequency: 8.38 versus 9.42 at week 8 AEs = no serious AEs					
RCT prospective (bupivacaine) (2018) [66]	n = 60 E = pain scale score from 9 to 1 (in GON block group) AEs = no serious AEs					
RCT (pulsed RF versus depomethylprednisolone) (2015) [63]	n = 9	n = 20 E = headache frequency from 3.140 (at baseline) to 1.810 (at 6 week) in steroid injection group; from 3.640 (at baseline) to 1.708 (at 6 week) in pulsed RF group AE = no serious AEs				
RCT (long- and rapid acting salts of betamethasone) (2005) [129]			n = 16 E = 85% of the patients AEs = transient pain at the injection site	n = 7 E = 85% of the patients AEs = transient pain at the injection site		

(Continued)

Table 2B. (Continued).

Study design	Migraine		Cluster headache (CH)			Other TACs	
	Episodic migraine (EM)	Chronic migraine (CM)	Episodic CH	Chronic CH		SUNHA	Hemicrania continua
Open-label (bupivacaine) (2016) [67]	n = 78 E = attack frequency: from 15.73 (at baseline) to 4.52 (at month 3) in group GON blockade versus from 13.76 to 3.28 in group GON blockade + prophylactic medication; headache severity: from 8.26 to 5.16 (in group GON blockade) versus from 8.80 to 5.96 (in group GON blockade + prophylactic medication) AEs = no serious AEs						
Open-label (bupivacaine) (2017) [59]	n = 18 patients (22 aura symptoms) E = 86% of the aura symptoms AEs = no serious AEs						
Open-label retrospective (bupivacaine) (2017) [68]		n = 41 E = headache frequency: unilateral GON block: from 20.0 (at baseline) to 9.9 (at 3 month post-treatment) versus bilateral GON block: from 20.44 to 12.00; pain intensity: unilateral GON block: from 7.05 to 5.11 versus bilateral GON block: from 6.84 to 5.91 AEs = no serious AEs					
Open-label observational case series (high volume lidocaine+triamcinolone) (2018) [130]				n = 10 E = 100% of the patients (for mean of 65.1 days post-treatment pain-free period) AEs = no serious AEs			
Open-label prospective (methylprednisolone) (2014) [131]				n = 83 E = 57% of the patients AEs = tenderness at the injection site, neck stiffness, dizziness			
Open-label case series (GON and/or SON or trochlear area) (bupivacaine plus mepivacaine) (2012) [150]							n = 22 E = 100% of the patients (reduction in pain intensity) AEs = no serious AEs
Retrospective cohort study (bupivacaine, lidocaine) (2018) [69]	n= 562 E = 58% of the patients AEs = vasovagal symptoms, burning feeling at the injection site						
Retrospective analysis (betamethasone) (2012) [133]			n = 31	n = 29 E = 64.8% of the patients (after first injection) AEs = local pain, facial oedema, insomnia, acne, bradycardia, syncope			

(Continued)

Table 2B. (Continued).

	Migraine		Cluster headache (CH)		Other TACs	
Study design	Episodic migraine (EM)	Chronic migraine (CM)	Episodic CH	Chronic CH	SUNHA	Hemicrania continua
Prospective observational (triamcinolone plus bupivacaine) (2017) [134]			n = 61	n= 40 E = 83.2% of the patients AEs = no serious AEs		
Single-center retrospective comparative (GON blockade with methylprednisolone versus oral steroid with prednisone and dexamethasone) (2018) [132]			n = 29	n = 12 E = 82.7% of oral steroid encounters (n = 81) and 64.4% of GON injection encounters (n = 59) AEs = no AEs were recorded		

Abbreviations: AE = adverse event; CH = cluster headache; E = effectiveness (at least 50% improvement in headache frequency and/or intensity); GON = greater occipital nerve; n = number of the randomized patients; NRS = numeric rating scale; RCT = randomized multicenter double-blind controlled trial; SON = supraorbital nerve; SUNHA = short-lasting unilateral neuralgiform headache attacks; TAC = trigeminal autonomic cephalalgia; VAS = Visual Analogue Scale.

3.1.1.2. Transcutaneous SONS (the cefaly® device) in migraine. The Cefaly® device is a non-invasive TENS of the supraorbital branches of the trigeminal nerves (Tables 1 and 3). The first evidence that TENS has beneficial effects in migraine and muscle contraction headache (today known as tension-type headache) comes from 1985 [9]. The exact mechanism of its action is enigmatic; however, recent blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI) data have revealed functional antinociceptive modulation in the perigenual part of the right anterior cingulate cortex [10]. A fluorodeoxyglucose positron emission tomography (FDG-PET) study revealed that SONS by Cefaly® device increased the activity of the limbic system, and the orbitofrontal and anterior cingulate cortices in EM without aura patients. These results indicate that the proposed mechanism of Cefaly® might be the modulation of the descending pain control system of the trigeminovascular nociceptor in the trigemino-cervical complex [11,12].

This type of trigeminal nerve stimulation was the first to obtain the Food and Drug Administration's (FDA) approval for migraine therapy [12] (Table 3).

3.1.1.2.1. RCTs of transcutaneous SONS (the Cefaly® device) in EM. The first double-blind RCT (Prevention of Migraine Using the STS Cefaly® – the PREMICE study) of SONS for preventive treatment in 67 non-CM patients was performed at five Belgian tertiary headache clinics. The results showed that during the 3-month-long study period, the mean number of headache days decreased significantly compared to the placebo group without any notable AEs. The number of monthly migraine attacks, headache days, and acute antimigraine drug intake was also reduced in the treatment group [13] (Table 3). A post-marketing retrospective survey highlighted that a high number (n = 2,313) of EM patients were satisfied with the efficacy of Cefaly® as a prophylactic treatment and willing to purchase the device (54.4% of subjects). The rate of AEs was low and reversible, predominantly local paresthesia, and only 2% of subjects stopped the therapy due to AEs [2,14]. A recent double-blind randomized sham-controlled study conducted in migraineurs with or without aura (n = 106) revealed that a 1-h treatment session with Cefaly® significantly decreased the pain intensity only in migraine without aura attacks [15]. A recently published review article mentioned that some new studies with Cefaly® are ongoing, e.g. acute treatment of EM or CM (double-blind RCT) and prevention of CM (open-label) [2]. An online questionnaire survey among 413 Cefaly® customers for migraine prevention demonstrated that 88.6% of the patients also used the device as an acute treatment in 71.8% of their attacks. The conclusion was that migraine attacks were mitigated and the device was well tolerated during the headache phase [16].

Taken together, the Cefaly® device is effective, well tolerated, and safe, probably both as preventive and acute treatment in drug-resistant migraine sufferers.

3.1.1.3. Transcutaneous cervical VNS (the gammaCore® device) in migraine. VNS modulates the activation of the trigeminal nucleus caudalis (TNC) via inhibition of the vagal afferents to the trigemino-cervical complex (TCC) and with the excess glutamate levels in the TNC [17–22]. Preclinical experiments showed that the trigeminal system influenced the parasympathetic system via CGRP and CGRP receptor components in the SPG [23]. Furthermore, experimental data indicate that

Table 3. Data of the non-invasive (transcutaneous) and invasive (implantable) supraorbital nerve stimulation (SONS) studies in intractable primary headache disorders.

| Study design | Migraine | | Cluster headache (CH) | | Other TACs | |
	Episodic migraine (EM)	Chronic migraine (CM)	Episodic CH	Chronic CH	SUNHA	Hemicrania continua
RCT of transcutaneous SONS (the Cefaly® device) (The PREMICE study) (2013) [13]	n = 67 E = 38.1% of the patients AEs = none					
RCT of transcutaneous SONS (the Cefaly® device) (2013) [14]	n = 2313 E = 54.4% of the patients AEs = local paresthesia					
RCT of transcutaneous SONS (the Cefaly® device) (2018) [15]	n = 109 E = 59% of the patients AEs = no serious AEs					
Single-center combined implantable ONS and implantable SONS (2013) [52]		n = 14 E = 71% of patients AEs = lead migration				
Long-term functional outcome combined implantable ONS and implantable SONS (2016) [53]		n = 16 E = 50% of the patients AEs = lead migration, supraorbital lead allodynia, infection				

Abbreviations: AE = adverse event; E = effectiveness (at least 50% improvement in headache frequency and/or intensity); n = number of the randomized patients; ONS = occipital nerve stimulation; RCT = randomized multicenter double-blind controlled trial; SUNHA = short-lasting unilateral neuralgiform headache attacks; TAC = trigeminal autonomic cephalalgia; VAS = Visual Analogue Scale.

the trigeminal-autonomic reflex may be active in migraine attacks [24]. We also highlight that VNS inhibits the cortical spreading depression (CSD), which is the electrophysiological correlate of migraine aura [25]. The orexinergic system provides a possible connection between the pathomechanism of migraine and CH via the dorsal vagal complex and the posterior part of the hypothalamus [26–28].

The first beneficial clinical experience of the effect of VNS on migraine pain came from an epileptic patient who received an implantable VNS [29]. There are several possibilities for the stimulation of the vagal nerve in primary headaches, including the non-invasive (i.e. transcutaneous) stimulation of the cervical or auricular branch of the vagal nerve and invasive (i.e. surgically implanted) VNS. The gammaCore® device uses electrical impulses to influence the cervical branch of the vagus nerve by transcutaneous administration [30] (Tables 1 and 4).

3.1.1.3.1. RCTs of transcutaneous VNS (the gammaCore® device) in CM. The first prospective, multicenter, double-blind, sham-controlled pilot study (the EVENT study) for the prevention of CM (n = 59; mean age of 39.2 years) demonstrated that at 2 months 9.1% of the CM patients achieved more than 50% treatment response, whereas in the open-label phase, at 8 months, this response rate elevated to 46.7%. The common AEs included eye twitch (7%), facial pain and numbness (10%), gastrointestinal symptoms (10%), and upper respiratory tract infection (10%) [31] (Table 4).

3.1.1.3.2. RCTs of transcutaneous VNS (the gammaCore® device) in EM. A randomized, multicenter, sham-controlled trial (the PRESTO study) for the acute treatment of EM (with or without aura; n = 248) revealed an increased probability of achieving a pain-free state at 2-h post-stimulation without any serious AEs. The VNS-treated group was superior to sham at 30 min: 12.7% versus 4.2%; at 60 min: 21.0% versus 10.0%; and at 120 min: 30.4% versus 19.7% [32] (Table 4).

3.1.1.3.3. Open-label studies of transcutaneous VNS (the gammaCore® device) in CM. An open-label, single-arm, multicenter study of non-invasive VNS for the acute treatment of high-frequency EM (n = 14) and CM (n = 36) revealed that at 2 h after treatment 51.1% of the patients experienced a 50% or greater reduction in pain intensity. Some 35.4% of CM patients and 39.6% of high-frequency EM patients achieved pain-free status at 1 and 2 h, respectively. The observable AEs were tingling and pricking sensations at the stimulation site (in 67% of the treated patients) [20] (Table 4).

3.1.1.3.4. Open-label studies of transcutaneous VNS (the gammaCore® device) in EM. An open-label pilot study of non-invasive VNS for the acute treatment of EM (with or without aura; n = 30, 25 females and 5 males, median age of 39 years) revealed that 22% of the patients experienced beneficial effects. No serious AEs were reported, some moderate AEs were observed, like stiff neck, neck redness, shoulder pain or spasm, coughing, fatigue, dizziness, or joint pain [33] (Table 4). A preliminary open-label single-arm safety study in nine adolescents (13–18 years old) EM without aura patients revealed that 46.8% of their treated migraine attacks showed a beneficial result. No device-related AEs were observed [34]. For menstrual/menstrually related migraine patients (n = 56), an open-label non-invasive VNS study as mini-prophylaxis revealed that 39% of the subjects showed 50% or more

reduction in headache days. The number of menstrual/menstrually related migraine days per month significantly decreased (from baseline 7.2 to 4.7 days at the end of the treatment). There were no serious AEs reported [35].

3.1.1.3.5. Single-center studies of transcutaneous VNS (the gammaCore® device) in migraine (EM and CM). A prospective, observational, single-center, cohort study of acute and preventive treatment in EM and CM patients revealed that pain intensity in VAS reduced in EM from 8 to 3.5, whereas in CM from 8 to 5. The number of headache days declined in EM from 11.3 to 5.7 and in CM from 18.1 to 12.1. The trial also demonstrated significant improvements in Migraine Disability Assessment (MIDAS), Beck Depression Inventory (BDI), and Pittsburgh Sleep Quality Index. No serious AEs were observed [36] (Table 4).

Taken together, in drug-resistant migraine, the non-invasive stimulation of the cervical branch of the vagus nerve has a beneficial effect and it is safe and well tolerated [37].

3.1.1.4. Transcutaneous auricular VNS (the NEMOS® device) in migraine.
The NEMOS® device is an easily applicable and portable stimulator of the auricular branch of the vagus nerve. The ear electrode is similar to a hearing aid, and the stimulator is hand-held [2]. The proposed pathomechanism of auricular VNS is that it may stimulate the thick myelinated fibers of the auricular branch of the vagus nerve, which results in the activation of the nucleus of the solitary tract [38,39].

3.1.1.4.1. Single-center studies of transcutaneous VNS (the NEMOS® device) in CM. A randomized, parallel-group (1 Hz versus 25 Hz), monocentric, double-blind, controlled trial with 46 CM patients revealed that in the 1 Hz group 29.4% of the patients had 50% or greater reduction in headache days, versus in the 25 Hz group it was only 13.3%. The Headache Impact Test (HIT) and the MIDAS scores were significantly improved in both groups without differences. The treatment-related AEs appeared at the stimulation site, like mild or moderate pain, paresthesia, pruritus, erythema, ulcer, or scab [38] (Tables 1 and 4).

3.1.2. Invasive neurostimulation in migraine

3.1.2.1. Implantable ONS in migraine.
The pathomechanism of ONS in migraine is unclear, with both central and peripheral effects being possibly involved [40,41]. The anatomical background for this technique in migraine and TACs is that in the TCC, the second-order nociceptive neuron has a convergent synapse from the trigeminal (i.e. meningeal) part and from the spinal region (i.e., the central branch of the cervical 2 segment) [42–44]. The other possibilities point to the activation of afferent A-beta fibers and the modulation of the descending supraspinal pathways from the periaqueductal grey matter (PAG) and the rostral ventromedial medulla [45].

3.1.2.1.1. RCTs of implantable ONS in CM. A long-term (52-week) RCT demonstrated that surgically-implanted ONS significantly reduced the number of headache days by 7.7(±8.7) days in intractable CM patients (n = 125) and by 6.7(±8.4) days in the intent-to-treat (ITT) analyses of all patients (n = 157)

Table 4. Data of the non-invasive vagus nerve stimulation (VNS) studies in drug-refractory primary headache disorders.

Study design	Migraine		Cluster headache (CH)			Other TACs	
	Episodic migraine (EM)	Chronic migraine (CM)	Episodic CH	Chronic CH	SUNHA		Hemicrania continua
The gammaCore® device (cervical branch of the vagus nerve)							
RCT (for acute and preventive treatment) (the PREVA study) (2016) [19]				n = 97 E = 40% of the patients AEs = headache, nasopharyngitis, dizziness, oropharyngeal pain, neck pain			
RCT (for acute treatment) (the ACT1 study) (2016) [108]			n = 38 E = 34.2% of the patients AEs = burning, tingling, soreness, stinging, lip, or facial drooping	n = 22 E = failed AEs = burning, tingling, soreness, stinging, lip, or facial drooping			
RCT (for acute treatment) (the ACT2 study) (2018) [109]			n = 27 E = 48% AEs = not relevant	n = 65 E = 5% AEs = not relevant			
RCT prospective pilot (for prevention) (the EVENT study) (2016) [31]		n = 59 E = 9.1% (at 2 month) E = 46.7% (at 8 month) AEs = eye twitch, facial pain/numbness, gastrointestinal symptoms, upper respiratory tract infection					
RCT (for acute treatment) (the PRESTO study) (2018) [32]	n = 248 E = at 30 min: 12.7% versus 4.2%; at 60 min: 21.0% versus 10.0%; at 120 min: 30.4% versus 19.7% AEs = no serious AEs						
Open-label single-arm multicenter (for acute treatment) (2015) [20]		n = 36 (high-frequency EM n = 14) E = 51% (at 2 h after treatment) AEs = stinging and pricking sensation					
Open-label single-arm multiple-attack pilot (for acute treatment) (2014) [33]	n = 30 E = 22% (pain-free rate) AEs = neck twitching, raspy voice, redness at the device site						
Open-label preliminary single-arm safety (for acute treatment) (2017) [34]	n = 9 E = 46.8% of the treated migraine attacks AEs = none						
Open-label menstrual/menstrually-related mini-prophylaxis (2016) [35]	n = 56 E: 39% of patients AEs: no serious AEs						
Open-label real-world prospective clinical audit (2018) [145]		n = 23 E: 2 out of 23 patients (at least 30% reduction in headache days/episodes) AEs = no serious AEs		n = 12 E: 1 out of 12 patients (at least 30% reduction in headache days/episodes) AEs = no serious AEs	n = 2 E: none of the patients AEs = no serious AEs		n = 4 E: 2 out of 4 patients (at least 30% reduction in headache days/episodes) AEs = no serious AEs

(Continued)

Table 4. (Continued).

| Study design | Migraine | | Cluster headache (CH) | | SUNHA | Other TACs |
	Episodic migraine (EM)	Chronic migraine (CM)	Episodic CH	Chronic CH		Hemicrania continua
Single-center prospective observational cohort (for acute and preventive treatment) (2015) [36]	n = 10 E = VAS = 8 (at baseline) versus VAS = 3.5 (at 3 month post-treatment) E = headache days: 11.3 (at baseline) versus 5.7 (at 3 month post-treatment) AEs = no serious AEs	n = 10 E = VAS = 8 (at baseline) versus VAS = 5 (at 3 month post-treatment) E = headache days: 18.1 (at baseline) versus 8.1 (at 3 month post-treatment) AEs = no serious AEs				
Single-center (2017) [146]						n = 9 E = 78% of the patients AEs = no serious
The NEMOS® device (auricular branch of the vagus nerve) Single-center sandomized parallel-group double-blind (for prevention) (2015) [38]		n = 46 E = 29,4% of the patients (at 1 Hz); 13.3% of the patients (at 25 Hz) AEs = pain, paresthesia, pruritus, erythema, ulcer, or scab				

Abbreviations: AE = adverse event; CH = cluster headache; E = effectiveness (at least 50% improvement in headache frequency and/or intensity); n = number of the randomized patients; RCT = randomized multicenter double-blind controlled trial; SUNHA = short-lasting unilateral neuralgiform headache attacks; TAC = trigeminal autonomic cephalalgia; VAS = Visual Analogue Scale.

[20]. In this study, 65.4% of the ITT population reported excellent or good headache relief. The MIDAS scores were also reduced, and more than half of CM patients were satisfied with this method. Lead migration was the leading AE in the hardware-related category (13.9%), whereas persistent pain and/or numbness was the leading AE among biological events (18.2%) [46] (Tables 1 and 2(a)). Another RCT of ONS revealed that suprathreshold stimulation evoked better pain relief than subthreshold stimulation (1.98(±1.56) versus 5.65(±2.11)) in 15 CM patients. No changes in Short-Form-36 (SF-36) were reported. No serious AEs were detected, and no technical malfunction was presented [47]. An RCT from 2012 revealed that ONS did not meet the primary endpoint (at least 50% reduction in main daily headache intensity) in a large CM patient group (active n = 105; sham n = 52); however, there was a significant difference in the percentage of patients who showed 30% pain reduction, and there were also significant differences in the reduction of the number of headache days and in migraine-related disability compared to the sham-treated group. The most frequent biological AE was persistent pain and/or paresthesia at the implant site (13.1% in active group versus 8.4% in control group). The most common hardware-related AE was lead migration (14% in active group versus 4.7% in control group) [48].

3.1.2.1.2. Open-label studies of implantable ONS in CM.

A prospective, long-term (7-year), open-label, uncontrolled, observational ONS study in 37 refractory CM patients revealed that pain, based on the VAS evaluation, decreased by 4.9 ± 2.0 points. Systemic AEs were not observed [49] (Table 2(a)). An open-label, prospective, cohort study showed that 28.5% of 35 refractory CM patients showed 50% or greater reduction in the daily attack frequency or pain severity. AEs were not mentioned [50].

3.1.2.1.3. Cross-over studies of implantable ONS in CM.

A prospective, randomized, cross-over study with ONS showed 54–60% reduction in 'Stimulation ON' compared to 'Stimulation OFF', both in the number and severity of headache attacks in CM. Only a few AEs were reported (2 infections and 3 lead migrations). The limitations of this study were the single center, the small number (n = 34) of patients, and the missing control group [51] (Table 2(a)).

3.1.2.1.4. Single-center studies of implantable ONS in CM.

A single-center (institutional) experience with combined implantable ONS and SONS revealed a 50% or greater decrease in pain severity in 71% of the CM patients (n = 14). Fifty percent of the patients experienced resolution of migraine-associated symptoms. The main AE was lead migration (42.8%) [52] (Table 2(a)). A long-term (from 5 to 80 months) functional outcome dual implantable ONS and implantable SONS study revealed that 8 out of 16 CM patients had a positive response defined as more than 50% of improvement in headache, quality of life, and functional outcome scores MIDAS and BDI. The main AEs included lead migration (42.8%), supraorbital lead allodynia (21.4%), and infection (14.2%), with a consequent high reoperation rate (35.7%) [53]. A long-term (6-year) retrospective study (carried out in two large tertiary referral centers) revealed that 53% of refractory CM patients (n = 25) reported 50% or greater reduction in headache intensity and/or frequency at long-term

follow-up. This study included refractory occipital neuralgia patients as well (n = 3), who reported more than 50% reduction in pain intensity at 28–31 months. The most frequent AE was lead displacement [54]. An observational, single-center experience study revealed an improvement in pain intensity by numeric rating scale (NRS) in CM patients at the 3-month and 12-month follow-up (NRS at baseline: 9.8(±0.7); at 3 months 5.0(±1.6); at 12 months: 5.7(±2.6)). Lead migration was the most common side effect [55].

Overall, the application of implantable ONS represents a promising therapeutic option in refractory CM cases.

3.1.2.2. Implantable cervical VNS in migraine

3.1.2.2.1. Retrospective studies of implantable VNS in epileptic patients with headache.

In the time period from 2012 to the present, an RCT with implantable VNS in purely primary headache disorder patients has not been published, in consistence with a recent review in the field [56]. A large (n = 325) retrospective clinical study demonstrated that implantable VNS had beneficial effects on daily headache/migraine intensity (VAS = 5.4 in the VNS group versus 7.8 in the group on best medical treatment) and affective/cognitive pain perception (21 in the VNS group versus 16 in the group on best medical treatment) in patients with drug-resistant focal epilepsy [57] (Table 4).

3.2. Nerve or ganglion blockades in migraine

3.2.1. GON blockade in migraine

3.2.1.1. RCTs of GON blockade with chemical agents in CM.

A placebo-controlled study of bilateral GON blockade (with 1.5 mL of 0.5% bupivacaine diluted in 1 mL of saline) in 44 CM patients revealed significantly decreased headache days from the baseline to third month (21.0 versus 6.3 days) compared to placebo (i.e. saline) treatment (20.9 versus 19.1 days). The pain intensity decreased from 8.9 to 6.3 in the treatment group, whereas in the placebo group from 8.7 to 8.6. No serious AEs were observed, only local pain at the site of injection, vertigo, and nausea occured [58] (Table 2(b)). A short-term (one-week) RCT in 36 CM patients demonstrated that bilateral GON blockade with bupivacaine (with 2 mL of 0.5% bupivacaine) was effective (i.e. the number of headache days of any pain intensity decreased from 4.9 to 3.4 in the treated group). This study also reported that the pressure pain thresholds increased after the blockade and decreased after placebo. Only a few AEs were reported, including presyncope and transient stinging sensation at the puncture site [59]. A prospective, randomized, placebo-controlled, double-blind pilot study of ultrasound-guided unilateral GON blockade (with 1.5 mL of 0.5% bupivacaine) in refractory CM without aura patients (n = 32) revealed that pain intensity decreased from VAS = 3.93 (pre-injection) to VAS = 1.55 (post-injection). The ultrasound-guided technique enabled a more accurate localization of the nerve. No serious AE was observed, only one patient suffered vaso-vagal syncope [60]. A RCT of GON blockade in CM patients (n = 84) using 1.5 mL of 0.5% bupivacaine diluted in 1 mL of saline (four times once per week) demonstrated that the number of headache days decreased from

18.1 (at baseline) to 8.8 (at 1 month), whereas the VAS score decreased from 8.4 to 2.1. The observed AEs were local pain at the site of injection and vertigo [61]. A multicenter, randomized, double-blind, comparative-effectiveness study (pulsed RF versus 2.75 mL injection containing 1 mL of 0.5% bupivacaine, 1 mL of 2% lidocaine, and 0.75 mL of 40 mg/mL depo-methylprednisolone) including 81 participants with occipital neuralgia or migraine (EM and CM) with occipital nerve tenderness revealed a greater pain relief in the pulsed RF group compared to the steroid injection group; without any serious associated AEs [62].

3.2.1.1.1. RCTs of GON blockade with chemical agents in mixed or unspecified migraine. An RCT of GON blockade using 2.5 mL of 0.5% bupivacaine plus 0.5 mL (20 mg) of methylprednisolone in episodic and chronic migraineurs (n = 70; between 18 and 75 years) for short-term preventive treatment revealed no difference in at least 50% reduction in the headache day frequency in active and placebo groups. The main AE was injection site pain (12% of the study subjects) [64] (Table 2(b)). An RCT conducted to compare the preventive effect of GON blockade with 1.0 mL of lidocaine 2% plus 0.5 mL of saline versus 1.0 mL of 2% lidocaine plus 0.5 mL of triamcinolone in migraine patients (n = 24 versus 24) demonstrated efficacy for both groups in terms of pain severity, pain frequency, and analgesic use at 2, 4, and 8 weeks post-treatment; however, no difference was revealed between the therapies. No serious AEs were observed in either group [65]. A prospective RCT conducted in an emergency department in patients with acute migraine attack (n = 60) demonstrated that GON blockade (1 mL of 0.5% bupivacaine plus 1 mL of normal saline) was superior to placebo (2 mL of normal saline; pain scale score: from 9 to 1 versus from 8 to 3 at 45 min after the injection). The GON blockade group did not differ from the IV dexketoprofen (50 mg) and IV metoclopramide (10 mg) groups at 45 min after treatment. No serious AEs were detected [66].

3.2.1.1.2. Open-label studies of GON blockade with chemical agents in EM. An open-label study that compared purely GON blockade with bupivacaine (2 mL; 0.25%) versus GON blockade plus prophylactic medication (amitriptyline 25 mg/day, topiramate 100 mg/day, or venlafaxine 150 mg/day) in migraineurs without aura showed significant improvement in headache frequency and severity in both groups, but there was no difference between the two groups. The attack frequency decreased from 15.73 (at baseline) to 4.52 (at month 3) in the GON blockade group versus from 13.76 to 3.28 in the GON blockade + prophylactic medication group, whereas headache severity was reduced from 8.26 to 5.16 in the GON blockade group versus from 8.80 to 5.96 in the GON blockade + prophylactic medication group. There were no serious AEs reported [67] (Table 2(b)). An open-label clinical trial of bilateral GON blockade with bupivacaine (2 mL, 0.5%) for the acute treatment of migraine patients with prolonged or persistent aura (n = 18 patients and 22 episodes with aura) revealed that complete response without early recurrence was achieved in 50% (n = 11) and with 24-h recurrence in 9.1% (n = 2) of the cases, whereas partial (greater than 50%) improvement was achieved in 27.3% (n = 6) of the cases. No serious AEs were reported [62].

3.2.1.1.3. Open-label studies of GON blockade with chemical agents in CM. A retrospective, open-label trial comparing unilateral and bilateral GON blockade using 1.5 mL of 0.5% bupivacaine plus 1 mL of saline in CM patients (n = 41; 23 unilateral and 18 bilateral) demonstrated no difference between the two groups regarding the frequency, severity, or duration of headache at 3 months post-treatment. The bilateral application was not superior to the unilateral one. No serious AEs were found [68].

3.2.1.1.4. Cohort studies of GON blockade with chemical agents in EM. A large retrospective cohort study of GON blockade with bupivacaine (6.3 mL, 0.25%; 2.5 mL, 0.5%) and/or lidocaine (2.4 mL, 1%) used for the acute treatment of migraine headache reported an 50% or greater pain reduction in 58% of the patients (n = 562; 423 women and 139 men; mean age of 58.6 years). Only a few AEs occurred, such as vasovagal symptoms and burning sensation at the injection site [69].

Overall, GON chemical blockade is a simple, applicable, efficacious, safe, well-tolerated, and cost-effective therapeutic option in drug-resistant migraine [70,71]. Treatment-related AEs are mild and of low frequency (Table 2(b)).

3.2.2. SPG blockade (with chemical agents) in migraine

The hypothesized mechanism of SPG modulation in migraine is the alteration of sensory processing in the TCC [72,73]. The modulation of SPG function, e.g. by means of chemical block, neurolysis, RF ablation, or neurostimulation in primary headache patients has shown some beneficial effects [3]. SPG stimulation is a minimally invasive method: the electrode, which has a wireless remote-controlled system (the Pulsante SPG Microstimulator System®), is implanted transorally into the pterygopalatine fossa [2] (Tables 1 and 5).

3.2.2.1. RCTs of SPG blockade with chemical agents in CM. A double-blind, parallel-arm, placebo-controlled, randomized pilot study showed that in 41 CM patients, bupivacaine (0.5%) versus saline repetitive injection into the SPG with Tx360® device (twice a week for 6 weeks) demonstrated significantly decreased headache intensity (NRS scores: 4.20 versus 2.85 at 24-h post-treatment). The bupivacaine study group was associated with a reduction in acute medication use and an improved quality of life. The most common AEs were the following: lacrimation (30%), bad taste (26%), mouth numbness (22%), and nasal irritation (15%) [74] (Table 5). The follow-up of the above trial, which was a long-term (6-month-long), double-blind, parallel-arm, placebo-controlled, randomized pilot study, revealed that the number of headache days decreased from 23.15 (at baseline) to 17.44 (at 1-month post-treatment). There was a statistical difference at 1 month and 6 months. The frequent AEs were taste disturbances, lacrimation, and oral numbness [75].

3.2.2.1.1. Open-label studies of SPG blockade with chemical agents in migraine. A prospective, open-label, uncontrolled study in 10 intractable CM patients was performed with bilateral percutaneous infrazygomatic administration of BoNTA-hemagglutinin complex (total dose of 50 IU) in patients under local anesthesia using a novel surgical navigation device (MultiGuide® device). The efficacy outcome was

Table 5. Data of the sphenopalatine ganglion (SPG) stimulation and blockade studies in drug-refractory primary headache disorders.

Study design	Migraine		Cluster headache (CH)		SUNHA	Other TACs
	Episodic migraine (EM)	Chronic migraine (CM)	Episodic CH	Chronic CH		Hemicrania continua
Electrical stimulation of SPG Multicenter RCT (the PATHWAY CH-I study) (2013) [126]				n = 32 E = 68% of the patients AEs = loss of sensation in the maxillary nerve region		
Long-term open-label follow-up of the PATHWAY CH-I study (attack remission) (2016) [123]				n = 33 E = 30% of the patients at least one episode of complete attack remission AEs = no serious AEs		
Long-term open-label follow-up of the PATHWAY CH-I study (effectiveness) (2017) [127]				n = 33 E = 61% of the patients AEs = no serious AEs		
The PATHWAY R-1 register study (2018) [128]			n = 7 E = 71.4% (frequency) AEs = not detailed	n = 78 E = 65% AEs = 73% postoperative sequelae		
Radiofrequency (RF) ablation of SPG Prospective open-label follow-up (pulsed RF) (2016) [137]			n = 13 E = 85% AEs = no seriousAEs			
Case series (2015) [138]			n = 3 E = 33% AEs = no serious AEs	n = 3 E = 2 out of 3 patients no pain relief after pulsed RF; 3 out of 3 patients pain-free after continuous RF + SPG blockade		
Ganglion (SPG) blockade with chemical agents RCT pilot (bupivacaine) (2015) [74]		n = 41 E = 4.20 versus 2.85 NRS score AE = lacrimation, nasal irritation, mouth numbness, bad taste				
Long-term RCT pilot (bupivacaine) (2015) [75]		n = 41 E = 17.44 versus 22.82 headache days at 1 month post-treatment AE = lacrimation, taste disturbances, oral numbing				
Prospective open-label uncontrolled (onabotulinumtoxinA) (2017) [139]		n = 10 E = 80% AE = local discomfort in the face and jaw				
Retrospective open-label uncontrolled (lidocaine) (2018) [77]		n = 55 E = 78.2% of the patients AEs = no serious AEs				

(Continued)

Table 5. (Continued).

Study design	Migraine		Cluster headache (CH)		SUNHA	Other TACs
	Episodic migraine (EM)	Chronic migraine (CM)	Episodic CH	Chronic CH		Hemicrania continua
Prospective open-label uncontrolled (onabotulinumtoxinA) (2016) [139]				n = 10 E = 50% AE = epistaxis, accomodation problem		
Retrospective single-center open-label (absolute alcohol) (2014) [140]			n = 14 E = 76.5% AE = no serious AE			
Case report (bupivacaine) (2016) [151]					n = 1 E = frequency: from 7/7 (baseline) to 2/7 (at week 4) and 0/7 (at week 6); intensity: VAS = 6/10 (at baseline) to 1/10 (at week 4) and 0/10 (at week 6) AE = no serious AE	

Abbreviations: AE = adverse event; E = effectiveness (at least 50% improvement in headache frequency and/or intensity); n = number of the randomized patients; NRS = numeric rating scale, RCT = randomized multicenter double-blind controlled trial; RF = radio frequency; SPG = sphenopalatine ganglion; SUNHA = short-lasting unilateral neuralgiform headache attacks; TAC = trigeminal autonomic cephalalgia; VAS = Visual Analogue Scale.

favorable: 8 out of 10 CM patients experienced a 50% or greater reduction in the number of moderate and severe headache days compared to baseline. All 10 patients experienced different AEs, including pain, swelling, and numbness (face, cheek), and jaw problem, none of them was serious [76] (Table 5). In a retrospective, open-label, uncontrolled SPG blockade trial in 55 migraine patients who received 2 ml of 2% lidocaine in each nostril by a Sphenocath® device for acute treatment, 78.2% of the patients were headache-free at 2-h post-treatment and only a few AEs were reported [77].

Overall, SPG blockade with chemical agents (i.e. bupivacaine or BoNTA-hemagglutinin complex) may have beneficial effects in medically refractory migraine patients.

3.3. BoNTA-hemagglutinin complex injection therapy in migraine

BoNTA is a purified neurotoxin produced by *Clostridium botulinum* bacteria. The effect of BoNTA in the nervous system is the specific cleavage of synaptosomal membrane-associated protein 25 kDa (SNAP-25) [78–80]. In clinical testing, it has been revealed that BoNTA diminished the interictal CGRP serum level in CM patients and was also able to reduce central sensitization [4,81–83]. The non-toxic components of the two forms of BoNTA (onabotulinum toxin A and abobotulinumtoxin A) each include a hemagglutinin [80]. Two RCTs, the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and 2, demonstrated that BoNTA-hemagglutinin complex reduced the monthly headache days in CM patients [84,85]. The recommended injection fixed-sites are frontal, temporal, occipital, and neck muscles, and the recommended fixed-doses are totally 155–195 units (U)/cycle (one cycle is 12 weeks) [4,86–88]. The latest Cochrane Database meta-analysis, which includes 28 trials (4190 participants) – the longest treatment duration was three cycles of injections – concluded that BoNTA-hemagglutinin complex treatment in CM reduced the number of migraine days per month by 2 days compared with placebo at 24 weeks (−8.4 days on BoNTA-hemagglutinin complex group; versus −6.6 days in placebo group), and no serious AEs were reported [89]. BoNTA-hemagglutinin complex is a medication approved by the FDA for the prevention of CM, and it is effective and safe, both in RCTs and in real-life studies [90,91].

3.4. CGRP- or CGRP receptor-targeted monoclonal antibody treatment in migraine

In a classical clinical experiment, *Edvinsson* and his co-workers elegantly demonstrated the function of CGRP during migraine attack [92,93]. The pathomechanism of migraine is unknown, but the activation and sensitization of the trigemino-vascular system via neuropeptides like CGRP and pituitary adenylate cyclase-activating polypeptide (PACAP) have crucial roles [94–99]. The center of the trigeminovascular system is the trigeminal ganglion, which has numerous CGRP-like immunopositive nerve cells, and it is not protected by the blood-brain barrier; therefore, it can be an ideal peripheral target for monoclonal antibodies (mAbs) in migraine therapy [100–104]. New genetic engineering techniques have opened up the possibility of developing fully humanized mAbs targeting CGRP and CGRP receptors [94,105]. The recent **overviews** summarized the efficacy outcome (50% or greater reduction in migraine days) of CGRP-related mAbs in EM **and CM patients**. The route of administration is parenteral (subcutaneous or intravenous). The CGRP receptor-targeted erenumab (AMG334) reached 46% versus placebo, while CGRP-targeted eptinezumab (ALD403) 61%, galcanezumab (LY2951742) 63%, and fremanezumab (TEV48125) 53% versus placebo in EM patients. The most frequent AE was upper respiratory tract infection, and there were no serious AEs [94,104]. Eptinezumab treatment in CM patients achieved a significant reduction in monthly migraine days compared to placebo (PROMISE 2 study) [106]. In fremanezumab-treated CM patients, the number of headache hours during study weeks 9–12 was significantly reduced compared to that in the placebo group. In the HALO CM fremanezumab trial, a higher rate of patients associated with a reduction of at least 50% in the average number of headache days per month was observed in the treated group compared to the placebo group. Galcanezumab treatment in CM patients (REGAIN trial) resulted in a significant decrease in the number of monthly headache days compared to controls [106].

4. Cluster headache

CH is one of the TACs. Typical features of CH attacks are strictly unilateral, very severe pain in orbital, supraorbital, and/or temporal areas. The head pain lasts 15–180 min and occurs from once every other day to eight times a day, and is typically associated with ipsilateral autonomic symptoms, such as conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis and/or ptosis, and/or eyelid edema. Restlessness or agitation may be present [5]. Its two main forms are episodic CH (ECH) and chronic CH (CCH).

4.1. Neurostimulation in CH

4.1.1. Non-invasive neurostimulation in CH
4.1.1.1. Transcutaneous cervical VNS (the gammaCore® device) in CH. The rationale of VNS in CH is based on the observation that the strong parasympathetic activation during CH attack is linked to the anatomical connection of the trigeminal system with the autonomic nervous system through the TCC. The superior salivatory nucleus (parasympathetic nucleus of the facial nerve) receives synaptic input from the central branch of the trigeminal ganglion. The consequence of its activation is the excitation of the SPG, which results in the release of parasympathetic neuropeptides (such as vasoactive intestinal polypeptide) to the pericranial vasculature [103,107].
4.1.1.1.1. RCTs of transcutaneous VNS (the gammaCore® device) in CH. A prospective, open-label RCT (the PREVA study) of transcutaneous VNS in CCH patients (n = 97) reported that the number of CH attacks per week significantly decreased compared to the control group (5.9 versus 2.1). Around 40% of the treated patients showed a response rate of 50% or greater. The most common AEs were headache (8%), dizziness (6%), oropharyngeal pain (6%), and neck pain

(6%) [19] (Table 4). A randomized, double-blind, sham-controlled study of VNS for the acute treatment of ECH and CCH patients (n = 60;the ACT1 study, conducted in the USA) revealed that only the ECH but not CCH patients experienced beneficial effects (ECH: 34.2% versus 10.6%; CCH: 13.6% versus 23.1%). The device-related AEs were burning, tingling, soreness, stinging at the application site (2.7%), and lip or facial drooping, pulling, or twitching (11.0%) [108]. A new extended RCT, the ACT2 study, in a European setting drew similar results. The total cohort of 92 ECH and CCH patients demonstrated no significant difference between non-invasive VNS (14%) and placebo stimulation (12%). The VNS treatment was superior to sham in ECH but not in CCH [109]. Regarding the economic aspect, the cost-effectiveness of the non-invasive VNS (the gammaCore® device) for the acute treatment of both ECH and CCH was superior to the standard of care [110,111].

Overall, in refractory CH, transcutaneous cervical VNS showed promising effect without any serious AE.

4.1.2. Invasive neurostimulation in CH
4.1.2.1. Implantable ONS in CH.
The central effect of implantable ONS is based on its potential to modulate the pain matrix, hence returning the associated hypermetabolism to a normal level, as measured by FDG-PET in CCH patients [112]. Evidence indicates the metabolic activation of different anatomical regions of the pain matrix in various primary headache disorders [42,112,113]. We underline the observation, however, that in CCH patients, ONS normalized the alteration in metabolism in each examined brain regions except the ipsilateral hypothalamus [112], the activation of which may have a crucial role in the generation of a CH attack [114]. In the CCH patients, after the cessation of ONS, attack recurrence is high, probably due to the lack of modulation of the activation of the hypothalamus [1,42,112].

4.1.2.1.1. RCTs of implantable ONS in CH and mixed headache.
The ICON study (the first blinded trial of peripheral pain neuromodulation in medically intractable CCH), which is still ongoing, will present some data from a double-blind set-up [40,45,115]. (Table 2(a)). A long-term (8.5-year) RCT indicated that migraine, CH, and miscellaneous headache patients (n = 29) responded well to ONS. Headache frequency was decreased by 18%, severity by 27%, and MIDAS by 50%. In CCH patients, four of five patients reported good effects. With regard to AEs, the lead revision was the most common one (58%) [116].

4.1.2.1.2. Open-label studies of implantable ONS in CH.
An open-label prospective cohort study of 33 CCH patients showed the beneficial effect of the method (54.5% of the patients reached 50% or more reduction in attack frequency) [50].

A long-term (median follow-up of 6.1 years) monocentric open-label ONS study demonstrated that 66.7% of the 35 drug-resistant CCH patients presented 50% or greater reduction in headache number per day. The most frequent AEs were battery depletion (70%) and electrode migration (20%) [117] (Table 2(a)).

4.1.2.1.3. Single-center studies of implantable ONS in CH.
The results of the prospective single-center but long-term (mean follow-up 20 months) study in intractable CCH or migraine showed high response rates (89% at short term and 78% at long term) to bilateral ONS. However, it appears to be a costly therapy (mean treatment cost is 28,186 EURO per case) [118] (Table 2(a)). Another single-center, long-term follow-up (1–8-year) study revealed that 8 out of 16 drug-resistant CCH patients became asymptomatic with bilateral ONS, whereas 2 patients changed from the chronic to episodic subtype, and 4 out of 16 patients showed more than 50% improvement in the reduction of the number of headache attacks. The frequent AEs were electrode migration, battery replacement, and local infection [119].

4.1.2.1.4. Observational studies of implantable ONS in CH.
A large, observational, prospective study in medically intractable CCH patients (n = 67) revealed that 59% of the patients reached a decrease in attack frequency of 50% or greater by ONS. A high percentage (70%) of the patients responded to the treatment. Moreover, as regards the secondary endpoints, the HIT-6, the MIDAS, and the Hospital Anxiety Depression Scale scores were significantly improved, and the use of prophylactic drug treatment decreased in 40% of patients. Only minor AEs were observed in 33% of the treated group [120] (Table 2(a)).

Overall, the results of ONS treatment in drug-resistant CCH patients demonstrated that the majority (i.e. two-thirds) of the subjects responded well to the treatment (50% or greater improvement in frequency and/or intensity); however, it is noteworthy that these were only observational studies [40,121]. A recent systematic review with meta-analysis concluded that the number of RCTs of ONS for intractable primary headache disorders is extremely low, and further research and high-level studies are needed [122]. ONS is an effective treatment compared to a placebo treatment. It is a promisingly useful but invasive and costly therapeutic option for drug-refractory primary headache disorders [50,122]. The common and frequent side effects of ONS are lead migration and local inflammation [42,45]. The currently available study results suggest that ONS is a valuable procedure with significant hardware- and non-hardware-related AEs even in experienced hands. In the near future, large, rigorous and well-designed high-level RCTs are needed.

4.1.2.2. Implantable SPG stimulation (the Pulsante SPG microstimulator system®) in CH.
Parasympathetic storming (lacrimation, rhinorrhoea, nasal congestion, and eyelid edema) is associated with trigemino-autonomic headache attacks (such as in CH) and some migraine attacks [73]. The anatomical center of this phenomenon is the SPG, which has connections to the trigemino-vascular system via the trigemino-parasympathetic reflex and also to the hypothalamus [2,123–125]. Despite the significant clinical parasympathetic activation and sympathetic dysfunction (i.e. ptosis and miosis), the origin of the pain and the connection with the SPG are not well characterized [124].

4.1.2.2.1. RCTs of SPG electrical stimulation in CH.
The first European clinical trial of acute treatment for CCH patients (n = 32; the PATHWAY CH-I study) demonstrated that 25% of the patients achieved more than 50% pain relief, and 36% of the CCH patients reported a more than 50% reduction in attack frequency, whereas 7% experienced both [126]. The reported

AEs were sensory disturbances (hypesthesia, paresthesia, dysesthesia, and allodynia) in the 81% of the patients, and pain affecting the face, temporomandibular joint, nose, or incision site in 38% of the patients [126] (Table 5). A long-term (24-month), open-label follow-up of the PATHWAY CH-I study regarding attack remission revealed that 30% of the CCH patients (n = 33) experienced at least one episode of complete attack remission. The pain-free period was at least one month. No serious AE was mentioned [123]. The evaluation of the long-term effectiveness in the same study cohort demonstrated that 45% of the CCH patients were acute responders and 33% of them was frequency responder; this yield a total responder rate of 61% [127]. The PATHWAY R-1 registry (open-label, prospective, post-marketing) study of SPG stimulation in ECH (n = 7) and CCH (n = 78) patients revealed that 68% of all patients were responders. In CCH patients, 65% of the patients showed 50% or greater response, either in term of the reduction in the attack intensity or attack frequency. In ECH patients, 71.4% (n = 5/7) responded well to the SPG neurostimulation therapy in terms of frequency; however, only 28.6% (n = 2/7) experienced an acute response. It was reported that 59% and 67% of all patients were HIT-6 and SF-36 responders, respectively. Regarding the AEs, 73% of all patients reported postoperative sequela, which were mild-to-moderate and resolved within 2–3 months [128].

Overall, SPG neurostimulation is a promising therapeutic option for intractable CH, mainly in its chronic form, with limitations due to its invasive nature.

4.2. Nerve or ganglion blockades in CH

4.2.1. GON blockade in CH

4.2.1.1. RCTs of GON blockade (with chemical agents) in CH.
A double-blind, placebo-controlled, ipsilateral GON blockade trial was conducted with a mixture of rapid-acting salt of betamethasone (disodium phosphate, 5.26 mg) and a long-acting salt of betamethasone (dipropionate 12.46 mg) and 0.5 mL of 2% xylocaine in ECH (n = 16) and CCH (n = 7) patients. A single dose of GON blockade completely diminished the CH attacks in more than 80% of CH patients in the verum group. The most common AE was transient pain at the injection site [129].

4.2.1.1.1. Open-label studies of GON blockade (with chemical agents) in CCH.
An open-label observational case series (n = 10) GON blockade study using high-volume (9 mL) lidocaine and triamcinolone (1 mL) in CCH patients demonstrated that all patients had complete pain relief for an average of 65.1 days post-injection. Smoking history did not alter the treatment response. No serious AEs were reported except for one patient who developed avascular necrosis of the hip [130] (Table 2(b)). A prospective open-label study with unilateral GON blockade (with methylprednisolone) in CCH patients (n = 83) demonstrated that 57% of the patients reached at least 50% pain relief (42% of them achieved complete response) after the first GON blockade. Regarding AEs, 34% of the sample population reported tenderness at the injection site, neck stiffness, or dizziness [131].

4.2.1.1.2. Single-center studies of GON blockade (with chemical agents) in CH.
A retrospective comparative single-center study for short-term prophylaxis of ECH and CCH comparing GON blockade with methylprednisolone to an oral steroid (prednisone or dexamethasone) revealed that 82.7% of the oral steroid encounters (n = 81) compared to 64.4% of GON injection encounters (n = 59) experienced complete or partial treatment response. No AEs were recorded [132].

4.2.1.1.3. Retrospective studies of GON blockade (with chemical agents) in CH.
A retrospective analysis with unilateral or bilateral GON blockade (121 injections in 60 ECH or CCH patients with betamethasone) revealed that after the first blockade 64.8% of the patients showed favorable treatment response. The reported AEs were local pain and steroid-related symptoms (e.g. facial edema, sleeping disorders, or acne), bradycardia, and syncope [133].

4.2.1.1.4. Prospective studies of GON blockade (with chemical agents) in CH.
A prospective observational study with single GON blockade (triamcinolone plus bupivacaine) in ECH (n = 61) and CCH (n = 40) patients revealed that 83.2% of the patients had a complete or partial response. No serious AEs occurred, only tiredness was reported [134].

Overall, the GON chemical blockade showed beneficial effect and it was well tolerated in the drug-refractory CH study population [135,136]. It can be performed on an outpatient basis [45].

4.2.2. SPG blockade in CH

4.2.2.1. Open-label studies of SPG blockade (with RF ablation) in CH.
A prospective, open-label, follow-up (12–30 months) study revealed that 11 out of 13 ECH patients and 1 out of 3 CCH patients experienced a pain-free state within an average of 6.3 days following the computerized tomography-guided pulsed RF treatment, with no serious AEs reported [137] (Table 5).

4.2.2.1.1. Case series of SPG blockade (with RF ablation) in CCH.
In a case series, two out of three CCH patients reported no pain relief after infrazygomatically pulsed RF treatment. After this unsuccessful procedure, the patients underwent continuous RF treatment with a corticosteroid (40 mg of methylprednisolone) and a local anesthetic (1 ml of 1% lidocaine) injection into the pterygopalatine fossa, which resulted in complete pain relief in all of the patients [138] (Table 5).

4.2.2.1.2. Open-label studies of SPG blockade (with chemical agents) in CH.
A prospective, open-label, uncontrolled pilot study with a follow-up of 24 weeks in 10 CCH patients demonstrated that a single symptomatic side transnasal injection of onabotulinumtoxinA (25 IU or 50 IU) under generalized anesthesia resulted in at least 50% reduction in attack frequency compared to the baseline in 50% of the patients. Regarding the safety outcome, 70% of the headache patients experienced AEs, including accommodation problems and epistaxis (anterior and posterior) [139] (Table 5). A retrospective, single-center, open-label study in CH patients (n = 14) revealed that percutaneous neurolysis with 1 ml absolute alcohol under local anesthesia and computer tomography guidance with an infra- or suprazygomatic approach was beneficial, as there was 50% or greater pain relief in 76.5% of the patients without any serious AEs [140].

Overall, in medically refractory CH patients, SPG blockade (with RF ablation or chemical agents) is effective, safe, and well tolerated.

4.3. BoNTA-hemagglutinin complex injection therapy in CH

A number of clinical trials using BoNTA-hemagglutinin complex as prophylaxis in CCH patients have been reported [141]; however, only a single trial followed the PREEMPT study protocol until now [142]. In this open-label, non-randomized, single-center study, a greater than 50% reduction in headache minutes was reached in 58.8% of the refractory CCH patients. The pain intensity was also significantly reduced in this patient population [142].

5. TACs other than CH

The TACs share the clinical features of unilateral headache and cranial autonomic features, which are ipsilateral to the headache [5]. Short-lasting unilateral neuralgiform headache attacks (SUNHA) are moderate or severe in intensity, strictly unilateral, lasting seconds to minutes, occurring at least once a day and usually associated with prominent lacrimation and redness of the ipsilateral eye [5]. Its two subtypes are short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), both of them can be episodic or chronic [5]. These are rare disorders, the prevalence of SUNCT is 6.6/100.000 persons and SUNA five times less frequent [143]. Hemicrania continua (HC), either remitting or unremitting subtypes, is a persistent, strictly unilateral pain, associated with ipsilateral autonomic features and/or with restlessness or agitation. HC responds exclusively to indomethacin [5,144].

5.1. Non-invasive (i.e. transcutaneous) cervical VNS (the gammaCore® device) in TACs other than CH

5.1.1. Open-label studies of transcutaneous cervical VNS in mixed headache (CM and TACs)

A real-world, open-label, prospective, clinical audit evaluated 41 refractory chronic primary headache patients after non-invasive cervical VNS for preventive and abortive treatment. The beneficial effects of VNS in these patients were surprisingly low. In CM patients only 2 out of 23, in CCH 1 out of 12, in HC 2 out of 4, and none of the SUNA patients (n = 2) reported a beneficial effect, which was defined as at least 30% reduction of headache days/episodes. There were no serious AEs observed. Otherwise, patients reported transient hoarseness/sore throat, red skin on the face and on the neck, increased frequency of bowel movements/flatus, and facial twitching [145] (Table 4).

5.1.1.1. Single-center studies of transcutaneous cervical VNS in TACs other than CH. In rare indomethacin-sensitive TACs such as HC (n = 9) and paroxysmal hemicrania (n = 6), a monocentric clinical study demonstrated that in the indomethacin non-tolerant patients the transcutaneous cervical

VNS, as an alternative or adjunctive therapy, showed beneficial effects (78% of the HC patients reported reduced severity of continuous pain) [146] (Table 4).

5.2. Implantable ONS in TACs other than CH

Recent multivariate analysis revealed that SUNCT and SUNA, among other refractory chronic primary headache patients, showed a high likelihood of response to ONS [50,147].

5.2.1. Open-label studies of ONS in TACs other than CH

A long-term, follow-up (median of 38 months), prospective, open-label ONS study in nine medically intractable headache patients (SUNCT n = 6; SUNA n = 3) demonstrated beneficial effects (4 patients pain-free; 4 patients 81–99% improvement; 1 patient non-responder). The AEs were electrode migration and muscle pain over the leads in 1 case per each [143,148] (Table 2(a)). An open-label, long-term follow-up, prospective series of 16 intractable HC patients showed beneficial effects of ONS. Half of the patients (8 out of 16) exhibited high (>50%) response rates (yielding a mean 48.9% reduction in monthly headache days) to bilateral ONS treatment. It is mentionable that the use of indomethacin dramatically (65.1%) decreased in those HC patients who continued to take the drug [144] (Table 2(a)). Another small-subject-number (n = 7 SUNCT and SUNA patients) study reported ONS to be highly effective and demonstrated a favorable safety profile [149].

5.3. Peripheral nerve blockades (including GON blockade) in TACs other than CH

5.3.1. Open-label studies of peripheral nerve blockades in HC

In an open-label case series, indomethacin-unresponsive or -intolerant HC patients (n = 22) were treated with GON and/or SON or trochlear area blockade with bupivacaine plus mepivacaine. They experienced total or partial improvement in pain intensity immediately, which lasted from 2 to 10 months in all the patients, without any serious AEs [150] (Table 2(b)).

5.4. SPG blockade in TACs other than CH

5.4.1. Case report of SPG blockade in HC

The case of a 52-year-old female patient with drug-resistant and indomethacin-intolerated HC was reported, who was treated with repetitive (twice a week for 6 weeks) SPG blockade with bupivacaine (0.6 mL; 0.5%) with a Tx360® device. She experienced beneficial effects both in terms of the frequency and intensity of her headache at week 6 post-treatment [151] (Table 5).

6. Conclusion

Refractory primary headaches, as chronic pain syndromes, have harmful impacts on patients' daily lives. Despite the fact that our incomplete knowledge about the pathogenesis of headache disorders expands on a daily basis, there is still no significant progress in marketed drug treatments. Peripheral neurostimulation and nerve and ganglion blockades may

provide proper therapeutic approaches to drug-resistant migraine, CH, and other TACs. No data from meta-analyses or systematic reviews are available in this field. The levels of evidence and the grades of the recommendation have not yet been defined as regards the neuromodulatory techniques in primary headaches, and as such, evidence-based therapeutic guidelines are missing in the current literature. Therefore, we have categorized the available data based on the different designs of the clinical trials they come from, reflecting the level of the existing evidence.

The concept of our summary statements is based on the quality of clinical evidence and the level of invasiveness. As summary statements, in drug-refractory EM, either non-invasive (i.e. transcutaneous) approaches (including ONS, SONS, and cervical VNS) or the minimally invasive GON blockade with chemical agents can be recommended as the first choice. No RCTs have been published with invasive methods in EM. In intractable CM, as being non-invasive, transcutaneous cervical VNS and GON blockade might be offered as the first choice, whereas invasive (i.e. implantable) ONS, combined ONS+SONS, and transcutaneous auricular VNS techniques can be offered as the second choice. In intractable ECH, transcutaneous cervical VNS can be offered as the first choice, whereas invasive electrical stimulation of SPG as the second choice. In intractable CCH, transcutaneous cervical VNS can be offered as the first choice, whereas invasive electrical stimulation of SPG and transcutaneous ONS can be offered as the second choice.

7. Expert opinion

The multifactorial nature of primary headache disorders and their, as yet, undetermined pathomechanisms lead to therapeutic difficulties. In the case of migraine, the currently available preventive drug treatments are inefficient, because only 30–50% of the patients respond well to them [152]. Furthermore, the low tolerability ratio and drug-related AEs strongly limit the recommended acute pharmacotherapies. Management of migraine is incompletely resolved [153]. All other forms of primary headaches face similar difficulties.

The different neuromodulation methods, including peripheral and central neurostimulation and nerve and ganglion blockades, provide us with favorable alternative therapeutic approaches. One of the main advantages of these novel techniques is that they can be combined with conventional and evidence-based recommended medications. We emphasize that the invasive neuromodulatory techniques should be restricted to refractory primary headache patients, whereas non-invasive methods can be offered to non-refractory ones as well. Socio-economically, we should underline their cost-effectiveness. The majority of these techniques can be performed in outpatient units. However, we highlight that there are still some areas of uncertainty with regards to the optimal way of performing GON blockade for migraine, because of the paucity of knowledge about the best local anesthetics to use, as well as about the optimal dosage and volume. Based on the data from RCTs in this field, we may recommend 1.5–2.5 mL of 0.5% bupivacaine.

The limitation of these neuromodulatory techniques is that the precise mechanism of their effect (i.e. influencing or inhibiting the activation of the trigeminovascular system) is weakly established, both at the preclinical and clinical level. Current evidence for these methods allows only a very narrow therapeutic indication (i.e. only medically refractory primary headaches). Based on the collected data of their safety issues, it is hard to spread them in a wider indication, both in acute and preventative scopes. On the other hand, the BoNTA-hemagglutinin complex injection therapy in CM and treatments using fully humanized mAbs targeting the CGRP or the CGRP receptor in migraine are already available on the market. These therapies associated with very good efficacy and safety features are easy to use, and they have a chance to move implantable devices down the treatment pathway in the near future.

Until now, based on the literature, predominantly open-label studies have been conducted instead of double-blind trials. The number of RCTs is surprisingly low. The difficulties of the blind neuromodulation studies are that the patients feel paresthesia during the active phase; therefore, patients can easily realize when the stimulator is 'ON' versus 'OFF' (sham).

There is a need to develop technically innovative, less invasive, and more user-friendly strategies. Real-life studies are warranted in order to get valuable results, not only in strictly selected but in the average patient population. The latest meta-analysis of the efficacy and safety of BoNTA-hemagglutinin treatment in CM revealed that it reduced the number of migraine days per month by 2 days compared with placebo after 24 weeks (−8.4 days in the BoNTA-hemagglutinin complex group versus −6.6 days in the placebo group). Therefore, future therapeutic options can be the combination of BoNTA-hemagglutinin complex with GON blockade, ONS, SONS, or transcutaneous VNS.

The pathomechanism of primary headache disorders is incompletely elucidated; however, some evidence points to the role of neuropeptides in the process, particularly CGRP and PACAP. Moreover, preclinical and clinical data increasingly associate the tryptophan-kynurenine pathway with the genesis of migraine headache. The classical migraine-related neuropeptide is CGRP. To date, only the fully humanized mAbs targeting CGRP or its receptors have shown up in the therapeutic palette of the prophylactic treatment of EM and CM. A challenging question remains the safety of the long-term use of these chemical agents, namely whether they have negative impacts on cardiovascular, bowel, endocrine, skin, and bone functions.

Future perspectives are to achieve personally tailored medical approaches in this particular patient population. The ultimate goal is to find genetic and/or neuroimaging biomarkers among primary headache patients in order to obtain correct indications for different neuromodulatory techniques, which can serve to maintain an optimal quality of life for headache sufferers.

7.1. Five-year view

At present, the main handicap of neuromodulation is the absence of the evidence-based proof of efficacy. In the near future, there is a need for well-designed and strictly organized large, long-term follow-up, randomized, multicenter, placebo-controlled clinical trials. The results of the primary and secondary endpoints should be interpreted with high-level statistical

analysis. In the far future, the scientific community should press the companies to create and use sham stimulation that is not associated with sensory disturbances to achieve clear data. A mobile health application system should be built-up, which can provide a bidirectional data exchange between headache patients and health-care professionals. Migraineurs treated with neurostimulators should aim to improve their self-management activities. It may also be suggested to create a web-based tele-monitoring platform in order to allow physicians to improve the complex management of their patients.

The old group of small molecule CGRP receptor antagonists (i.e. gepants) such as olcegepant, telcagepant, MK-3207, and BI44370T have already been tested in clinical studies and have shown promise in terms of efficacy; however, the liver toxicity associated with long-term use restricts their wide-spread clinical application. The latest innovation created three new gepants (rimegepant, ubrogepant, and atogepant), which have passed phase III clinical trials and they are ahead of final registration. We have a hope that the newly synthesized CGRP receptor antagonists will be efficacious and safe as well as [94].

PACAP has wide biological distribution within the peripheral and central nervous system. It might have a fundamental role in the pathomechanism of migraine and CH [154]. Intravenously administered PACAP1-38 induced migraine-like attacks in patients with migraine without aura [155]. Specific PACAP1-38 plasma level alterations were demonstrated during ictal and interictal periods of migraineurs, and also in ECH patients [156,157]. Based on these observations, early-phase RCTs are currently running to evaluate the efficacy and safety of mAbs targeting PAC1-receptor or PACAP1-38 [158]. Recent preclinical and clinical studies have revealed a new possible aspect of migraine management by influencing the kynurenine pathway [159–163]. Experimental studies with electrically activated trigeminovascular system pointed to a direct link between PACAP and the kynurenine pathway in rats [164]. In CM sufferers, altered serum levels of different kynurenine metabolites have been demonstrated [165]. Fully humanized mAbs targeting CGRP or CGRP-receptors and also antibodies against PACAP or PAC1-receptors, and possibly even kynurenine pathway-related therapeutic approaches may provide us with a novel, innovative opportunity either alone or in combination with different neuromodulation techniques in intractable drug-resistant headache patients.

Acknowledgments

Funding

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Schwedt TJ, Vargas B. Neurostimulation for treatment of migraine and cluster headache. Pain Med. 2015;16(9):1827–1834.
2. Schuster NM, Rapoport AM. New strategies for the treatment and prevention of primary headache disorders. Nat Rev Neurol. 2016;12 (11):635–650.
•• An important summary of the updated management of primary headache disorders.
3. Zagami AS. Treatment of the patient with refractory headache. Curr Pain Headache Rep. 2018;22(4):23.
•• A paper summarizing all the important aspects of the treatment of refractory primary headaches.
4. May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. Nat Rev Neurol. 2016;12(8):455–464.
5. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211.
6. Robbins MS, Lipton RB. Transcutaneous and percutaneous neurostimulation for headache disorders. Headache. 2017;57(Suppl 1):4–13.
•• It is a well-structured review with high scientific impact concerning non-invasive neurostimulation in headache disorders.
7. Liu Y, Dong Z, Wang R, et al. Migraine prevention using different frequencies of transcutaneous occipital nerve stimulation: a randomized controlled trial. J Pain. 2017;18(8):1006–1015.
8. Nguyen JP, Nizard J, Kuhn E, et al. A good preoperative response to transcutaneous electrical nerve stimulation predicts a better therapeutic effect of implanted occipital nerve stimulation in pharmacologically intractable headaches. Neurophysiol Clin. 2016;46 (1):69–75.
9. Solomon S, Guglielmo KM. Treatment of headache by transcutaneous electrical stimulation. Headache. 1985;25(1):12–15.
10. Russo A, Tessitore A, Esposito F, et al. Functional changes of the perigenual part of the anterior cingulate cortex after external trigeminal neurostimulation in migraine patients. Front Neurol. 2017;8:282.
11. Magis D, D'Ostilio K, Thibaut A, et al. Cerebral metabolism before and after external trigeminal nerve stimulation in episodic migraine. Cephalalgia. 2017;37(9):881–891.
12. Schoenen J, Coppola G. Efficacy and mode of action of external trigeminal neurostimulation in migraine. Expert Rev Neurother. 2018;18(7):545–555.
•• This is an excellent overview of the efficacy and safety of the Cefaly® device in migraine.
13. Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology. 2013;80(8):697–704.
14. Magis D, Sava S, d'Elia TS, et al. Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the cefaly(R) device in headache treatment: a survey of 2,313 headache sufferers in the general population. J Headache Pain. 2013;14:95.

15. Chou DE, Shnayderman Yugrakh M, Winegarner D, et al. Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. Cephalalgia. 2018;333102418811573.

16. Penning S, Schoenen J. A survey on migraine attack treatment with the CEFALY((R)) device in regular users. Acta Neurol Belg. 2017;117 (2):547–549.

17. Beekwilder JP, Beems T. Overview of the clinical applications of vagus nerve stimulation. J Clin Neurophysiol. 2010;27(2):130–138.

18. Lyubashina OA, Sokolov AY, Panteleev SS. Vagal afferent modulation of spinal trigeminal neuronal responses to dural electrical stimulation in rats. Neuroscience. 2012;222:29–37.

19. Gaul C, Diener HC, Silver N, 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):534–546.

20. Barbanti P, Grazzi L, Egeo G, et al. Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: an open-label study. J Headache Pain. 2015;16:61.

21. Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. J Inflamm Res. 2018;11:203–213.

22. Leone M, Cecchini AP. Central and Peripheral neural targets for neurostimulation of chronic headaches. Curr Pain Headache Rep. 2017;21(3):16.

23. Csati A, Tajti J, Tuka B, et al. Calcitonin gene-related peptide and its receptor components in the human sphenopalatine ganglion – interaction with the sensory system. Brain Res. 2012;1435:29–39.

24. Csati A, Tajti J, Kuris A, et al. Distribution of vasoactive intestinal peptide, pituitary adenylate cyclase-activating peptide, nitric oxide synthase, and their receptors in human and rat sphenopalatine ganglion. Neuroscience. 2012;202:158–168.

25. Chen SP, Ay I, de Morais AL, et al. Vagus nerve stimulation inhibits cortical spreading depression. Pain. 2016;157(4):797–805.

26. Ferguson AV, Samson WK. The orexin/hypocretin system: a critical regulator of neuroendocrine and autonomic function. Front Neuroendocrinol. 2003;24(3):141–150.

27. Holland P, Goadsby PJ. The hypothalamic orexinergic system: pain and primary headaches. Headache. 2007;47(6):951–962.

28. Strother LC, Srikiatkhachorn A, Supronsinchai W. Targeted orexin and hypothalamic neuropeptides for migraine. Neurotherapeutics. 2018;15(2):377–390.

29. Sadler RM, Purdy RA, Rahey S. Vagal nerve stimulation aborts migraine in patient with intractable epilepsy. Cephalalgia. 2002;22 (6):482–484.

30. Yuan H, Silberstein SD. Vagus nerve and vagus nerve stimulation, a comprehensive review: part I. Headache. 2016;56(1):71–78.

31. Silberstein SD, Calhoun AH, Lipton RB, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: the EVENT study. Neurology. 2016;87(5):529–538.

32. Tassorelli C, Grazzi L, de Tommaso M, et al. Noninvasive vagus nerve stimulation as acute therapy for migraine: the randomized PRESTO study. Neurology. 2018;91(4):e364–e373.

33. Goadsby PJ, Grosberg BM, Mauskop A, et al. Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. Cephalalgia. 2014;34(12):986–993.

34. Grazzi L, Egeo G, Liebler E, et al. Non-invasive vagus nerve stimulation (nVNS) as symptomatic treatment of migraine in young patients: a preliminary safety study. Neurol Sci. 2017;38(Suppl 1):197–199.

35. Grazzi L, Egeo G, Calhoun AH, et al. Non-invasive Vagus Nerve stimulation (nVNS) as mini-prophylaxis for menstrual/menstrually related migraine: an open-label study. J Headache Pain. 2016;17(1):91.

36. Kinfe TM, Pintea B, Muhammad S, et al. Cervical non-invasive vagus nerve stimulation (nVNS) for preventive and acute treatment of episodic and chronic migraine and migraine-associated sleep disturbance: a prospective observational cohort study. J Headache Pain. 2015;16:101.

37. Redgrave J, Day D, Leung H, et al. Safety and tolerability of transcutaneous Vagus Nerve stimulation in humans; a systematic review. Brain Stimul. 2018;11(6):1225–1238.

• **This paper describes the safety issues of the non-invasive vagal nerve stimulation in headaches.**

38. Straube A, Ellrich J, Eren O, et al. Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial. J Headache Pain. 2015;16:543.

39. Mercante B, Ginatempo F, Manca A, et al. Anatomo-physiologic basis for auricular stimulation. Med Acupunct. 2018;30(3):141–150.

40. Trentman TL, Schwedt TJ. Occipital nerve stimulation and beyond: when is invasive peripheral stimulation for headaches appropriate? Expert Rev Neurother. 2016;16(3):237–239.

41. Martelletti P, Jensen RH, Antal A, et al. Neuromodulation of chronic headaches: position statement from the European Headache Federation. J Headache Pain. 2013;14:86.

•• **This article contains the crucial position statement of the European Headache Federation about neuromodulatory techniques in drug-refractory headaches.**

42. Magis D, Schoenen J. Advances and challenges in neurostimulation for headaches. Lancet Neurol. 2012;11(8):708–719.

43. Bartsch T, Goadsby PJ. Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. Brain. 2002;125(Pt 7):1496–1509.

44. Bartsch T, Goadsby PJ. Increased responses in trigeminocervical nociceptive neurons to cervical input after stimulation of the dura mater. Brain. 2003;126(Pt 8):1801–1813.

45. Ambrosini A, Schoenen J. Invasive pericranial nerve interventions. Cephalalgia. 2016;36(12):1156–1169.

46. Dodick DW, Silberstein SD, Reed KL, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: long-term results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia. 2015;35 (4):344–358.

47. Slotty PJ, Bara G, Kowatz L, et al. Occipital nerve stimulation for chronic migraine: a randomized trial on subthreshold stimulation. Cephalalgia. 2015;35(1):73–78.

48. Silberstein SD, Dodick DW, Saper J, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia. 2012;32 (16):1165–1179.

49. Rodrigo D, Acin P, Bermejo P. Occipital nerve stimulation for refractory chronic migraine: results of a long-term prospective study. Pain Physician. 2017;20(1):E151–E159.

50. Miller S, Watkins L, Matharu M. Long-term follow up of intractable chronic short lasting unilateral neuralgiform headache disorders treated with occipital nerve stimulation. Cephalalgia. 2018;38 (5):933–942.

51. Serra G, Marchioretto F. Occipital nerve stimulation for chronic migraine: a randomized trial. Pain Physician. 2012;15(3):245–253.

52. Hann S, Sharan A. Dual occipital and supraorbital nerve stimulation for chronic migraine: a single-center experience, review of literature, and surgical considerations. Neurosurg Focus. 2013;35(3):E9.

53. Clark SW, Wu C, Boorman DW, et al. Long-term pain reduction does not imply improved functional outcome in patients treated with combined supraorbital and occipital nerve stimulation for chronic migraine. Neuromodulation. 2016;19(5):507–514.

54. Palmisani S, Al-Kaisy A, Arcioni R, et al. A six year retrospective review of occipital nerve stimulation practice–controversies and challenges of an emerging technique for treating refractory headache syndromes. J Headache Pain. 2013;14:67.

55. Notaro P, Buratti E, Meroni A, et al. The effects of peripheral occipital nerve stimulation for the treatment of patients suffering from chronic migraine: a single center experience. Pain Physician. 2014;17(3):E369–374.

56. Lendvai IS, Maier A, Scheele D, et al. Spotlight on cervical vagus nerve stimulation for the treatment of primary headache disorders: a review. J Pain Res. 2018;11:1613–1625.

57. Pintea B, Hampel K, Bostrom J, et al. Extended long-term effects of cervical vagal nerve stimulation on headache intensity/frequency and affective/cognitive headache perception in drug resistant

complex-partial seizure patients. Neuromodulation. 2017;20 (4):375–382.

58. Gul HL, Ozon AO, Karadas O, et al. The efficacy of greater occipital nerve blockade in chronic migraine: A placebo-controlled study. Acta Neurol Scand. 2017;136(2):138–144.

59. Cuadrado ML, Aledo-Serrano A, Navarro P, et al. Short-term effects of greater occipital nerve blocks in chronic migraine: A double-blind, randomised, placebo-controlled clinical trial. Cephalalgia. 2017;37(9):864–872.

60. Palamar D, Uluduz D, Saip S, et al. Ultrasound-guided greater occipital nerve block: an efficient technique in chronic refractory migraine without aura? Pain Physician. 2015;18(2):153–162.

61. Inan LE, Inan N, Karadas O, et al. Greater occipital nerve blockade for the treatment of chronic migraine: a randomized, multicenter, double-blind, and placebo-controlled study. Acta Neurol Scand. 2015;132(4):270–277.

62. Cuadrado ML, Aledo-Serrano A, Lopez-Ruiz P, et al. Greater occipital nerve block for the acute treatment of prolonged or persistent migraine aura. Cephalalgia. 2017;37(8):812–818.

63. Cohen SP, Peterlin BL, Fulton L, et al. Randomized, double-blind, comparative-effectiveness study comparing pulsed radiofrequency to steroid injections for occipital neuralgia or migraine with occipital nerve tenderness. Pain. 2015;156(12):2585–2594.

64. Dilli E, Halker R, Vargas B, et al. Occipital nerve block for the short-term preventive treatment of migraine: A randomized, double-blinded, placebo-controlled study. Cephalalgia. 2015;35 (11):959–968.

65. Kashipazha D, Nakhostin-Mortazavi A, Mohammadianinejad SE, et al. Preventive effect of greater occipital nerve block on severity and frequency of migraine headache. Global J Health Sci. 2014;6 (6):209–213.

66. Korucu O, Dagar S, Corbacioglu SK, et al. The effectiveness of greater occipital nerve blockade in treating acute migraine-related headaches in emergency departments. Acta Neurol Scand. 2018;138(3):212–218.

67. Inan N, Inan LE, Coskun O, et al. Effectiveness of greater occipital nerve blocks in migraine prophylaxis. Noro Psikiyatri Ars. 2016;53 (1):45–48.

68. Unal-Artik HA, Inan LE, Atac-Ucar C, et al. Do bilateral and unilateral greater occipital nerve block effectiveness differ in chronic migraine patients? Neurol Sci. 2017;38(6):949–954.

69. Allen SM, Mookadam F, Cha SS, et al. Greater occipital nerve block for acute treatment of migraine headache: a large retrospective cohort study. J Am Board Fam Med. 2018;31(2):211–218.

70. Zhang H, Yang X, Lin Y, et al. The efficacy of greater occipital nerve block for the treatment of migraine: A systematic review and meta-analysis. Clin Neurol Neurosurg. 2018;165:129–133.
   • **The authors give the basic principle of the greater occipital nerve block for the treatment of migraine.**

71. Tang Y, Kang J, Zhang Y, et al. Influence of greater occipital nerve block on pain severity in migraine patients: A systematic review and meta-analysis. Am J Emerg Med. 2017;35(11):1750–1754.

72. Vukovic Cvetkovic V, Jensen RH. Neurostimulation for the treatment of chronic migraine and cluster headache. Acta Neurol Scand. 2019;139(1):4-17.

73. Khan S, Schoenen J, Ashina M. Sphenopalatine ganglion neuromodulation in migraine: what is the rationale? Cephalalgia. 2014;34 (5):382–391.

74. Cady R, Saper J, Dexter K, et al. A double-blind, placebo-controlled study of repetitive transnasal sphenopalatine ganglion blockade with tx360((R)) as acute treatment for chronic migraine. Headache. 2015;55(1):101–116.

75. Cady RK, Saper J, Dexter K, et al. Long-term efficacy of a double-blind, placebo-controlled, randomized study for repetitive sphenopalatine blockade with bupivacaine vs. saline with the Tx360 device for treatment of chronic migraine. Headache. 2015;55(4):529–542.

76. Bratbak DF, Nordgard S, Stovner LJ, et al. Pilot study of sphenopalatine injection of onabotulinumtoxinA for the treatment of intractable chronic migraine. Cephalalgia. 2017;37(4):356–364.

77. Binfalah M, Alghawi E, Shosha E, et al. Sphenopalatine ganglion block for the treatment of acute migraine headache. Pain Res Treat. 2018;2516953:2018.

78. Turton K, Chaddock JA, Acharya KR. Botulinum and tetanus neurotoxins: structure, function and therapeutic utility. Trends Biochem Sci. 2002;27(11):552–558.

79. Frampton JE. Onabotulinumtoxin A (BOTOX(R)): a review of its use in the prophylaxis of headaches in adults with chronic migraine. Drugs. 2012;72(6):825–845.

80. De Boulle K, Fagien S, Sommer B, et al. Treating glabellar lines with botulinum toxin type A-hemagglutinin complex: a review of the science, the clinical data, and patient satisfaction. Clin Interv Aging. 2010;5:101–118.

81. Cernuda-Morollon E, Ramon C, Martinez-Camblor P, et al. OnabotulinumtoxinA decreases interictal CGRP plasma levels in patients with chronic migraine. Pain. 2015;156(5):820–824.

82. Cady R, Turner I, Dexter K, et al. An exploratory study of salivary calcitonin gene-related peptide levels relative to acute interventions and preventative treatment with onabotulinumtoxinA in chronic migraine. Headache. 2014;54(2):269–277.

83. Hollanda L, Monteiro L, Melo A. Botulinum toxin type a for cephalic cutaneous allodynia in chronic migraine: a randomized, double-blinded, placebo-controlled trial. Neurol Int. 2014;6(4):5133.

84. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010;30(7):793–803.

85. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010;30(7):804–814.

86. Szok D, Csati A, Vecsei L, et al. Treatment of chronic migraine with onabotulinumtoxina: mode of action, efficacy and safety. Toxins (Basel). 2015;7(7):2659–2673.

87. Tajti J, Szok D, Tuka B, et al. Botulinum neurotoxin–a therapy in migraine. Ideggyogy Szemle. 2012;65(3–4):77–82.

88. Vecsei L, Majlath Z, Szok D, et al. Drug safety and tolerability in prophylactic migraine treatment. Expert Opin Drug Saf. 2015;14 (5):667–681.

89. Herd CP, Tomlinson CL, Rick C, et al. Botulinum toxins for the prevention of migraine in adults. Cochrane Database Syst Rev. 2018;6:CD011616.

90. Tassorelli C, Tedeschi G, Sarchielli P, et al. Optimizing the long-term management of chronic migraine with onabotulinumtoxinA in real life. Expert Rev Neurother. 2018;18(2):167–176.

91. Negro A, Curto M, Lionetto L, et al. Chronic migraine treatment: from onabotulinumtoxin A onwards. Expert Rev Neurother. 2016;16 (10):1217–1227.

92. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol. 1990;28(2):183–187.

93. Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. Headache. 2017;57(Suppl 2):47–55.

94. Edvinsson L, Haanes KA, Warfvinge K, et al. CGRP as the target of new migraine therapies - successful translation from bench to clinic. Nat Rev Neurol. 2018;14(6):338–350.
   • **An outstanding summary of the latest CGRP-targeted therapeutic possibilities in migraine.**

95. Vecsei L, Lukacs M, Tajti J, et al. The therapeutic impact of new migraine discoveries. Curr Med Chem. 2018 May 29. doi: 10.2174/0929867325666180530114534.

96. Vecsei L, Tuka B, Tajti J. Role of PACAP in migraine headaches. Brain. 2014;137(Pt 3):650–651.

97. Tajti J, Szok D, Majlath Z, et al. Migraine and neuropeptides. Neuropeptides. 2015;52:19–30.

98. Tajti J, Pardutz A, Vamos E, et al. Migraine is a neuronal disease. J Neural Transm. 2011;118(4):511–524.

99. Tajti J, Szok D, Pardutz A, et al. Where does a migraine attack originate? In the brainstem. J Neural Transm. 2012;119(5):557–568.

100. Tajti J, Uddman R, Moller S, et al. Messenger molecules and receptor mRNA in the human trigeminal ganglion. J Auton Nerv Syst. 1999;76(2–3):176–183.

101. Eftekhari S, Salvatore CA, Johansson S, et al. Localization of CGRP, CGRP receptor, PACAP and glutamate in trigeminal ganglion. relation to the blood-brain barrier. Brain Res. 2015;1600:93–109.

102. Edvinsson L, Villalon CM, MaassenVanDenBrink A. Basic mechanisms of migraine and its acute treatment. Pharmacol Ther. 2012;136 (3):319–333.

103. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annu Rev Physiol. 2013;75:365–391.

104. Edvinsson L. Headache advances in 2017: a new horizon in migraine therapy. Lancet Neurol. 2018;17(1):5–6.

105. Vecsei L, Szok D, Csati A, et al. CGRP antagonists and antibodies for the treatment of migraine. Expert Opin Investig Drugs. 2015;24(1):31–41.

106. Dodick DW. CGRP ligand and receptor monoclonal antibodies for migraine prevention: evidence review and clinical implications. Cephalalgia. 2019;39(3):445–458.

107. Goadsby PJ. Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. Lancet Neurol. 2002;1(4):251–257.

108. Silberstein SD, Mechtler LL, Kudrow DB, 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):1317–1332.

109. Goadsby PJ, de Coo IF, Silver N, 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):959–969.

110. Morris J, Straube A, Diener HC, et al. Cost-effectiveness analysis of non-invasive vagus nerve stimulation for the treatment of chronic cluster headache. J Headache Pain. 2016;17:43.

111. Mwamburi M, Liebler EJ, Tenaglia AT. Cost-effectiveness of gammaCore (non-invasive vagus nerve stimulation) for acute treatment of episodic cluster headache. Am J Manag Care. 2017;23(16 Suppl):S300–S306.

112. Magis D, Bruno MA, Fumal A, et al. Central modulation in cluster headache patients treated with occipital nerve stimulation: an FDG-PET study. BMC Neurol. 2011;11:25.

113. Matharu MS, Bartsch T, Ward N, et al. Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain. 2004;127(Pt 1):220–230.

114. Goadsby PJ, May A. PET demonstration of hypothalamic activation in cluster headache. Neurology. 1999;52(7):1522.

115. Wilbrink LA, Teernstra OP, Haan J, et al. Occipital nerve stimulation in medically intractable, chronic cluster headache. The ICON study: rationale and protocol of a randomised trial. Cephalalgia. 2013;33 (15):1238–1247.

116. Brewer AC, Trentman TL, Ivancic MG, et al. Long-term outcome in occipital nerve stimulation patients with medically intractable primary headache disorders. Neuromodulation. 2013;16(6):557–562. discussion 563–554

117. Leone M, Proietti Cecchini A, Messina G, et al. Long-term occipital nerve stimulation for drug-resistant chronic cluster headache. Cephalalgia. 2017;37(8):756–763.

118. Mueller O, Diener HC, Dammann P, et al. Occipital nerve stimulation for intractable chronic cluster headache or migraine: a critical analysis of direct treatment costs and complications. Cephalalgia. 2013;33(16):1283–1291.

119. Lainez MJ, Guillamon E. Cluster headache and other TACs: pathophysiology and neurostimulation options. Headache. 2017;57 (2):327–335.

120. Fontaine D, Blond S, Lucas C, et al. Occipital nerve stimulation improves the quality of life in medically-intractable chronic cluster headache: results of an observational prospective study. Cephalalgia. 2017;37(12):1173–1179.

121. Leone M, Giustiniani A, Cecchini AP. Cluster headache: present and future therapy. Neurol Sci. 2017;38(Suppl 1):45–50.

122. Cadalso RT Jr., Daugherty J, Holmes C, et al. Efficacy of electrical stimulation of the occipital nerve in intractable primary headache disorders: a systematic review with meta-analyses. J Oral Facial Pain Headache. 2018;32(1):40–52.

• This review provides an overview of the current data of occipital nerve stimulation in pharmacoresistant primary headaches.

123. Barloese MC, Jurgens TP, May A, 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.

124. Ho KWD, Przkora R, Kumar S. Sphenopalatine ganglion: block, radiofrequency ablation and neurostimulation - a systematic review. J Headache Pain. 2017;18(1):118.

• An excellent overview of the blockade and electrical stimulation of the sphenopalatine ganglion.

125. Robbins MS, Robertson CE, Kaplan E, et al. The sphenopalatine ganglion: anatomy, pathophysiology, and therapeutic targeting in headache. Headache. 2016;56(2):240–258.

126. Schoenen J, Jensen RH, Lanteri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. pathway CH-1: a randomized, sham-controlled study. Cephalalgia. 2013;33(10):816–830.

127. Jurgens TP, Barloese M, May A, et al. Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache. Cephalalgia. 2017;37(5):423–434.

128. Barloese M, Petersen A, Stude P, et al. Sphenopalatine ganglion stimulation for cluster headache, results from a large, open-label European registry. J Headache Pain. 2018;19(1):6.

129. Ambrosini A, Vandenheede M, Rossi P, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain. 2005;118 (1–2):92–96.

130. Rozen TD. High-volume Anesthetic Suboccipital nerve blocks for treatment refractory chronic cluster headache with long-term efficacy data: an observational case series study. Headache. 2019;59 (1):56-62.

131. Lambru G, Abu Bakar N, Stahlhut L, et al. Greater occipital nerve blocks in chronic cluster headache: a prospective open-label study. Eur J Neurol. 2014;21(2):338–343.

132. Wei J, Robbins MS. Greater occipital nerve injection versus oral steroids for short term prophylaxis of cluster headache: a retrospective comparative study. Headache. 2018;58(6):852–858.

133. Gantenbein AR, Lutz NJ, Riederer F, et al. Efficacy and safety of 121 injections of the greater occipital nerve in episodic and chronic cluster headache. Cephalalgia. 2012;32(8):630–634.

134. Gaul C, Roguski J, Dresler T, et al. Efficacy and safety of a single occipital nerve blockade in episodic and chronic cluster headache: A prospective observational study. Cephalalgia. 2017;37 (9):873–880.

135. Leroux E, Valade D, Taifas I, et al. Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2011;10(10):891–897.

136. Martelletti P, Giamberardino MA, Mitsikostas DD. Greater occipital nerve as target for refractory chronic headaches: from corticosteroid block to invasive neurostimulation and back. Expert Rev Neurother. 2016;16(8):865–866.

137. Fang L, Jingjing L, Ying S, et al. Computerized tomography-guided sphenopalatine ganglion pulsed radiofrequency treatment in 16 patients with refractory cluster headaches: twelve- to 30-month follow-up evaluations. Cephalalgia. 2016;36(2):106–112.

138. Bendersky DC, Hem SM, Yampolsky CG. Unsuccessful pulsed radiofrequency of the sphenopalatine ganglion in patients with chronic cluster headache and subsequent successful thermocoagulation. Pain Pract. 2015;15(5):E40–45.

139. Bratbak DF, Nordgard S, Stovner LJ, et al. Pilot study of sphenopalatine injection of onabotulinumtoxinA for the treatment of intractable chronic cluster headache. Cephalalgia. 2016;36(6):503–509.

140. Kastler A, Cadel G, Comte A, et al. Alcohol percutaneous neurolysis of the sphenopalatine ganglion in the management of refractory cranio-facial pain. Neuroradiology. 2014;56(7):589–596.

141. Sostak P, Krause P, Forderreuther S, et al. Botulinum toxin type-A therapy in cluster headache: an open study. J Headache Pain. 2007;8(4):236–241.

142. Lampl C, Rudolph M, Brautigam E. OnabotulinumtoxinA in the treatment of refractory chronic cluster headache. J Headache Pain. 2018;19(1):45.

143. Lambru G, Matharu MS. SUNCT and SUNA: medical and surgical treatments. Neurol Sci. 2013;34(Suppl 1):S75–81.

144. Miller S, Watkins L, Matharu MS. Treatment of intractable hemicrania continua by occipital nerve stimulation. J Neurol Neurosurg Psychiatry. 2017;88(9):805–806.

145. Trimboli M, Al-Kaisy A, Andreou AP, et al. Non-invasive vagus nerve stimulation for the management of refractory primary chronic headaches: A real-world experience. Cephalalgia. 2018;38(7):1276–1285.

146. Tso AR, Marin J, Goadsby PJ. Noninvasive vagus nerve stimulation for treatment of indomethacin-sensitive headaches. JAMA Neurol. 2017;74(10):1266–1267.

147. Arca KN, Halker Singh RB. SUNCT and SUNA: an update and review. Curr Pain Headache Rep. 2018;22(8):56.

148. Lambru G, Shanahan P, Watkins L, et al. Occipital nerve stimulation in the treatment of medically intractable SUNCT and SUNA. Pain Physician. 2014;17(1):29–41.

149. Baraldi C, Pellesi L, Guerzoni S, et al. Therapeutical approaches to paroxysmal hemicrania, hemicrania continua and short lasting unilateral neuralgiform headache attacks: a critical appraisal. J Headache Pain. 2017;18(1):71.

150. Guerrero AL, Herrero-Velazquez S, Penas ML, et al. Peripheral nerve blocks: a therapeutic alternative for hemicrania continua. Cephalalgia. 2012;32(6):505–508.

151. Androulakis XM, Krebs KA, Ashkenazi A. Hemicrania continua may respond to repetitive sphenopalatine ganglion block: A case report. Headache. 2016;56(3):573–579.

152. Tfelt-Hansen P, Olesen J. Taking the negative view of current migraine treatments: the unmet needs. CNS Drugs. 2012;26(5):375–382.

153. Miller S, Matharu MS. Migraine is underdiagnosed and undertreated. Practitioner. 2014;258(1774):19–24, 12–13.

154. Tajti J, Tuka B, Botz B, et al. Role of pituitary adenylate cyclase-activating polypeptide in nociception and migraine. CNS Neurol Disord Drug Targets. 2015;14(4):540–553.

155. Schytz HW, Birk S, Wienecke T, et al. PACAP38 induces migraine-like attacks in patients with migraine without aura. Brain. 2009;132(Pt 1):16–25.

156. Tuka B, Helyes Z, Markovics A, et al. Alterations in PACAP-38-like immunoreactivity in the plasma during ictal and interictal periods of migraine patients. Cephalalgia. 2013;33(13):1085–1095.

157. Tuka B, Szabo N, Toth E, et al. Release of PACAP-38 in episodic cluster headache patients - an exploratory study. J Headache Pain. 2016;17(1):69.

158. Rubio-Beltran E, Correnti E, Deen M, et al. PACAP38 and PAC1 receptor blockade: a new target for headache? J Headache Pain. 2018;19(1):64.

159. Guo S, Vecsei L, Ashina M. The L-kynurenine signalling pathway in trigeminal pain processing: a potential therapeutic target in migraine? Cephalalgia. 2011;31(9):1029–1038.

160. Curto M, Lionetto L, Fazio F, et al. Fathoming the kynurenine pathway in migraine: why understanding the enzymatic cascades is still critically important. Intern Emerg Med. 2015;10(4):413–421.

161. Vecsei L, Szalardy L, Fulop F, et al. Kynurenines in the CNS: recent advances and new questions. Nat Rev Drug Discov. 2013;12(1):64–82.

162. Tajti J, Majlath Z, Szok D, et al. Novel kynurenic acid analogues in the treatment of migraine and neurodegenerative disorders: preclinical studies and pharmaceutical design. Curr Pharm Des. 2015;21(17):2250–2258.

163. Tajti J, Szok D, Nagy-Grocz G, et al. Kynurenines and PACAP in migraine: medicinal chemistry and pathogenetic aspects. Curr Med Chem. 2017;24(13):1332–1349.

164. Kortesi T, Tuka B, Tajti J, et al. Kynurenic acid inhibits the electrical stimulation induced elevated pituitary adenylate cyclase-activating polypeptide expression in the TNC. Front Neurol. 2017;8:745.

165. Curto M, Lionetto L, Negro A, et al. Altered kynurenine pathway metabolites in serum of chronic migraine patients. J Headache Pain. 2015;17:47.