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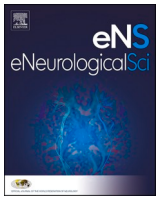

World neurology updates: Other primary headache disorder – Treatment

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After migraine, which accounts for some 94 % of primary care primary headache disorder presentations, few conditions rise to the level of "need-to-know". Cluster headache is probably the main consideration. In primary care, and to some extent in neurology practice, it could be argued that if a primary headache diagnosis other than migraine is considered, it might be simplest to refer to a headache medicine specialist. This naturally is a workforce consideration in any country. After migraine, the next likely form of headache that will cause a patient to seek medical advice, because it can be severe and disabling, is the group of Trigeminal Autonomic Cephalalgias (TAC). The TACs consists of four primary headache disorders – cluster headache, paroxysmal hemicrania (PH), hemicrania continua (HC), short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)/short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) [1]. These disorders share the common feature of lateralized headache with cranial parasympathetic autonomic reflex activation with prominent cranial autonomic symptoms including conjunctival injection, lacrimation, nasal congestion, rhinorrhea, and aural fullness.

Cluster headache is the most common of the TACs, varying in frequency from 1:1000 to 1:50,000 of the population [2]. Cluster headache presents with severe unilateral pain in the trigeminal distribution, primarily in the periorbital region, lasting typically from 15 up to 180 min, if untreated. The pain is often associated with ipsilateral cranial autonomic symptoms and patients are often restless and agitated. Attacks occur once every other day up to eight times per day, often waking the sufferer from sleep. In the most common form, called episodic cluster headache, the attacks (the bout) stop for periods of three months or more. Patients who do not have a remission period, or a remission period of less than 3 months, for at least 1 year are classified as chronic cluster headache [1]. The other TACs are characterized by the frequency and duration of their attacks and cranial autonomic symptoms (Table 1). The remarkable circadian and circannual periodicity of the disorder, as well as results from functional imaging studies, suggest, at the least, involvement of structures in, or proximate, to the hypothalamus [3]. The treatment of cluster headache will be the focus of this short review.

1. Treatment of cluster headache

The treatment of cluster headache can be divided into that of the acute attack and strategies to reduce attack frequency [4].

Acute attack treatment: Acute treatment for cluster headache includes subcutaneous sumatriptan 6 mg sc, intranasal sumatriptan 20 mg and zolmitriptan 5 mg, high flow oxygen with a non-rebreather mask and for episodic cluster – non-invasive vagus nerve stimulation (nVNS). For patients with greater than 2 attacks in a day, oxygen 100 % has been demonstrated to be effective [5] and is generally used at a flow rate of 12 to 15 L/min. Although sumatriptan and oxygen can both be prescribed as first line therapy, each has its own advantages and disadvantages, and patients can be prescribed both. While triptans do not have issues of portability that oxygen may have, they have important cardiovascular and cerebrovascular contraindications.

Preventive treatment- interim: While patients wait for preventive treatments to take effect, shorter term treatment may be helpful, or indeed sufficient when bout length is relatively short. This may consist of oral prednisone, such as 100 mg daily for 5 days tapered by 20 mg

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Table 1
Clinical features of trigeminal autonomic cephalalgias (adapted) [10].

Features	PH	HC	CH	SUNCT/SUNA
Gender Ratio (male to female)	1:1	1:2	3:1	1.5:1
Pain quality	Sharp/stab/throb	Baseline dull with worsening, throbbing or sharp	Sharp/stab/throb	Sharp/stab/throb
Duration	2–30 min	30 min - 3 days*	15–180 min	1–10 min
Restlessness during attack (%)	80	69	95	65
Circadian periodicity	Absent	Absent	Present	Absent
Triggers	–	–	Alcohol Nitroglycerin	Cutaneous
Acute treatment response	Indomethacin	Indomethacin	Oxygen Sumatriptan nVNS (ECH)	Intravenous lidocaine infusion
Preventive Treatment	Indomethacin Celecoxib Topiramate Melatonin Neuromodulation (nVNS)	Indomethacin Neuromodulation (nVNS)	Verapamil Galcanezumab Topiramate Melatonin Lithium Greater occipital nerve block	Lamotrigine Topiramate Gabapentin Lacosamide Oxcarbazepine Carbamazepine

ECH, episodic cluster headache; PH, Paroxysmal hemicrania; CH, Cluster headache; HC, Hemicrania continua; SUNCT/SUNA = Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; nVNS, non-invasive vagal nerve stimulation. *duration of worsenings

every 3 days, which has been shown to have efficacy as an adjunctive treatment to verapamil [6]. An equally effective, and somewhat less side effect prone approach, is unilateral greater occipital nerve "block", such as with 80 mg methylprednisolone with 2 mL of 2 % lidocaine [7]. Most recently, it has been shown in a randomized placebo-controlled trial that galcanezumab reduces attack frequency in episodic cluster headache [8].

Preventive Treatment- longer term: Several options exist for preventive treatment of cluster headache. Verapamil is the most commonly used first line medication, which has randomized clinical trial evidence albeit limited [4]. Verapamil is typically started at 80 mg three times a day after a baseline ECG, and can be increased by 80 mg every 2 weeks to response up to a maximum recommended dose of 320 mg three times a day. Up to one in five patients taking verapamil can develop arrhythmia, bradycardia or PR interval prolongation and patients should receive a baseline 12 lead ECG prior to starting treatment followed by at 10 days after each dose increment and every six months on a stable dose given heart block may develop [9]. Other options include lithium, which has some evidence yet is generally poorly tolerated, topiramate and melatonin.

Preventive treatment with neuromodulation: A range of neuromodulation approaches have been used in the treatment of cluster headache. These include non-invasive vagus nerve stimulation, sphenopalatine ganglion stimulation, occipital nerve stimulation and most rarely deep brain stimulation. Each has advantages and disadvantages, and are best deployed in expert centers.

2. Conclusion

The trigeminal autonomic cephalalgias are severe, disabling forms of primary headache disorders. The most common of these is cluster headache.

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Sina Marzoughi: Writing – original draft. **Peter J. Goadsby:** Conceptualization, Writing – review & editing.

Declaration of competing interest

Sina Marzoughi has no conflicts of interest.

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References

[1] Headache Classification Committee of the International Headache Society (IHS), The International Classification of Headache Disorders 38, 2018, pp. 1–211.
[2] K. Hagen, One-year prevalence of cluster headache, hemicrania continua, paroxysmal hemicrania and SUNCT in Norway: a population-based nationwide registry study, J. Headache Pain 25 (1) (2024) 30.
[3] D.Y. Wei, P.J. Goadsby, Cluster headache pathophysiology - insights from current and emerging treatments, Nat. Rev. Neurol. 17 (2021) 308–324.
[4] D.Y. Wei, M. Khalil, P.J. Goadsby, Managing cluster headache, Pract. Neurol. 19 (2019) 521–528.
[5] A.S. Cohen, B. Burns, P.J. Goadsby, High flow oxygen for treatment of cluster headache. A randomized trial, JAMA 302 (2009) 2451–2457.
[6] M. Obermann, S. Nagel, C. Ose, N. Sonuc, A. Scherag, P. Storch, et al., Safety and efficacy of prednisone versus placebo in short-term prevention of episodic cluster headache: a multicentre, double-blind, randomised controlled trial, Lancet Neurol. 20 (2021) 29–37.
[7] M.S. Robbins, A.J. Starling, T.M. Pringsheim, W.J. Becker, T.J. Schwedt, Treatment of cluster headache: the American headache society evidence-based guidelines, Headache 56 (2016) 1093–1106.
[8] P.J. Goadsby, D.W. Dodick, M. Leone, J.N. Bardos, T.M. Oakes, B.A. Millen, et al., Trial of Galcanezumab in prevention of episodic cluster headache, N. Engl. J. Med. 381 (2019) 132–141.
[9] A.S. Cohen, M.S. Matharu, P.J. Goadsby, Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy, Neurology 69 (2007) 668–675.
[10] D.Y.-T. Wei, J.J.Y. Ong, P.J. Goadsby, Overview of trigeminal autonomic Cephalalgias: Nosologic evolution, diagnosis, and management, Ann. Indian Acad. Neurol. 21 (Suppl. 1) (2018) S39–S44.