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REVIEW ARTICLE

Pharmacotherapy for Cluster Headache

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Abstract
Cluster headache is characterised by attacks of excruciating unilateral headache or facial pain lasting 15 min to 3 h and is seen as one of the most intense forms of pain. Cluster headache attacks are accompanied by ipsilateral autonomic symptoms such as ptosis, miosis, redness or flushing of the face, nasal congestion, rhinorrhoea, peri-orbital swelling and/or restlessness or agitation. Cluster headache treatment entails fast-acting abortive treatment, transitional treatment and preventive treatment. The primary goal of prophylactic and transitional treatment is to achieve attack freedom, although this is not always possible. Subcutaneous sumatriptan and high-flow oxygen are the most proven abortive treatments for cluster headache attacks, but other treatment options such as intranasal triptans may be effective. Verapamil and lithium are the preventive drugs of first choice and the most widely used in first-line preventive treatment. Given its possible cardiac side effects, electrocardiogram (ECG) is recommended before treating with verapamil. Liver and kidney functioning should be evaluated before and during treatment with lithium. If verapamil and lithium are ineffective, contraindicated or discontinued because of side effects, the second choice is topiramate. If all these drugs fail, other options with lower levels of evidence are available (e.g. melatonin, clomiphene, dihydroergotamine, pizotifen). However, since the evidence level is low, we also recommend considering one of several neuromodulatory options in patients with refractory chronic cluster headache. A new addition to the preventive treatment options in episodic cluster headache is galcanezumab, although the long-term effects remain unknown. Since effective preventive treatment can take several weeks to titrate, transitional treatment can be of great importance in the treatment of cluster headache. At present, greater occipital nerve injection is the most proven transitional treatment. Other options are high-dose prednisone or frovatriptan.

Key Points

Cluster headache treatment entails both fast-acting abortive treatment and preventive treatment.

Subcutaneous administration of sumatriptan has been proven to be the most effective abortive treatment.

Verapamil and lithium are the most widely used drugs in first-line preventive treatment.

1 Introduction

Cluster headache is considered the most severe primary headache disorder and is characterised by attacks of excruciating unilateral headache or facial pain lasting 15 min to 3 h [1]. Of patients who experience cluster headache, 55% have suicidal ideations, which highlights the extent of the pain and its impact on daily life [2]. Attacks can occur from every other day to up to eight times a day, with a tendency for nocturnal attacks. Typically, attacks are accompanied by ipsilateral autonomic symptoms such as ptosis, miosis, redness or flushing of the face, nasal congestion, rhinorrhoea, peri-orbital swelling and/or restlessness or agitation. Cluster headache was historically thought to be more prevalent among men than among women (ratio 3:1) [2, 3], but recent studies [4, 5] have reported a decreasing male predominance (ratio 2:1).

Cluster headache can be classified as chronic cluster headache (cCH) (15%) and episodic cluster headache (eCH) (85%). In eCH, the attacks occur in 'bouts' (clusters) that last from weeks to months and alternate with

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remission periods of months to years [6]. In cCH, remission periods are absent or last < 3 months for at least 1 year [1] (Table 1). Cluster headache exhibits a remarkable circadian pattern, with attacks often occurring at the same time of the day. Furthermore, a predilection for a circadian pattern exists, with attack tendency increased in autumn and spring [7].

Cluster headache treatment entails both fast-acting abortive treatment to effectively abort an ongoing attack and preventive treatment. Transitional treatment is fast acting, but the effect usually lasts only a couple of weeks; it can bridge the gap between the start of prophylactic medication and adequate drug titration. Current therapy mainly consists of pharmacotherapy, but neuromodulatory treatment methods such as occipital nerve stimulation [8, 9], non-invasive vagal nerve stimulation [10], sphenopalatine ganglion stimulation [11] and blockade [12] and local infiltration with anaesthetics and corticosteroids are becoming more and more available with increasing evidence of efficacy.

This article provides an overview of currently available pharmacological treatment for cluster headache. This is not a systematic review, but we have described current treatments and new emerging pharmacological treatments to the best of our knowledge. Since this is an overview of pharmacological treatment options for cluster headache, invasive and non-invasive neurostimulation treatment options are not discussed.

2 Pathophysiology

The exact pathophysiology of cluster headache remains unknown. Several structures have been found to contribute to cluster headache attacks: the trigeminovascular system, the parasympathetic nerve fibres and the hypothalamus [13]. The severe unilateral pain is thought to be mediated by the ophthalmic division of the trigeminal nerve. However, no effect on attack frequency was observed with complete trigeminal nerve root section [14]. Parasympathetic nerve fibre activation is triggered by the trigeminal nerve via the trigeminal autonomic reflex [15]. Activation of the parasympathetic nerve fibres induces autonomic symptoms. The aforementioned regularity and seasonality of cluster headache implicates hypothalamic involvement in its pathophysiology. Early imaging studies indeed showed hypothalamic activation in cluster headache attacks [16–19]. How this hypothalamic activation contributes to the generation of cluster headache attacks remains unclear, but the hypothalamus is currently regarded as the 'attack generator'.

Although no single gene has (yet) been identified in cluster headache, there is increasing evidence of a genetic component. Genetic studies indicate that first-degree relatives are 5–18 times more likely to have cluster headache, and second-degree relatives are one to three times more likely to have cluster headache.

Although cluster headache is a primary headache, cases of atypical cluster headache and even 'classic' cluster

Table 1 Diagnostic criteria for cluster headache according to the *International Classification Of Headache Disorders Third Edition* (ICHD-3)

Cluster headache
A. At least five attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min (when untreated)[a]
C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
conjunctival injection and/or lacrimation
nasal congestion and/or rhinorrhoea
eyelid oedema
forehead and facial sweating
miosis and/or ptosis
2. A sense of restlessness or agitation
D. Occurring with a frequency between one every other day and eight per day[b]
E. Not better accounted for by another ICHD-3 diagnosis
Episodic cluster headache
A. Attacks fulfilling criteria for cluster headache and occurring in bouts (cluster periods)
B. At least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥ 3 months
Chronic cluster headache
A. Attacks fulfilling criteria for cluster headache, and
B. occurring without a remission period, or with remissions lasting < 3 months, for at least 1 year

[a]During part, but less than half, of the active time-course of cluster headache, attacks may be less severe and/or of shorter or longer duration

[b]During part, but less than half, of the active time-course of cluster headache, attacks may be less frequent

headache secondary to underlying structural pathology have been described. A case review describing 63 cases of symptomatic cluster headache revealed that a significant proportion of secondary cases were associated with structural changes in the pituitary region and with arterial dissection [20].

Attention has recently shifted to structural and functional connectivity studies revealing changes in the pain matrix [21, 22]. Alterations in non-traditional pain-processing networks, including the hypothalamic–cerebellar network and occipital networks have also been reported [23–27].

3 Cluster Headache Treatment

The treatment of cluster headache can be divided into three treatment phases: a fast-acting abortive treatment, preventive drugs and transitional treatment to bridge the period between patients starting preventive drug dosages and the drugs asserting an effect. The main goal in cluster headache treatment should always be to prevent all attacks. Unfortunately, attack freedom cannot always be achieved, especially in patients with cCH. For these patients, it is vital to have effective attack treatment options and to achieve the best effect/side effect ratio in close collaboration with the patient.

3.1 Acute Treatment

The short duration and severity of cluster headache attacks call for a fast-acting abortive treatment, but, to date, drugs that can effectively treat cluster attacks are limited. Subcutaneous sumatriptan and/or high-flow oxygen are the acute treatment drugs of first choice. Table 2 summarises the drugs used for acute treatment.

3.1.1 Triptans

Subcutaneous sumatriptan (6 mg), a selective 5-hydroxytryptamine receptor agonist, is the most effective abortive treatment for cluster headache attacks [28, 29]. Pain relief is usually achieved in 75% of patients within 15 min, with one-third of patients reporting pain freedom. Triptans are generally well-tolerated. Chest symptoms and distal paraesthesia are the most common adverse events and can occur in up to 10% of patients. An early dose-comparison study reported no significant difference in pain relief between doses of 6 and 12 mg, with a higher adverse event rate in the group receiving 12 mg [29]. Only one prospective study investigated a lower dose (<6 mg) of sumatriptan in the treatment of cluster headache [30]. This study concluded that dosages of 2 and 3 mg could be effective in a subgroup of patients, but further studies are needed. The incidence of triptan-related serious cardiovascular events appears to be extremely low in patients without known cardiovascular disease [31].

In daily practice, patients with cluster headache experiencing daily attacks use multiple sumatriptan injections per day for a long time. Official guidelines state that no more than two injections per day can be used. However, evidence of a lack of safety with more than two injections per day is scarce. Two case reports described two patients with cluster headache using excessive dosages of sumatriptan for 15 years (first patient) and 11 months (second patient) without any serious adverse events [32, 33]. A later study showed no serious adverse events or electrocardiogram (ECG) abnormalities in 53 patients with cCH using more than two injections of sumatriptan daily for 2 years [34]. A study investigating the efficacy of sumatriptan injections in which 36 of 52 patients used more than the maximum daily dosage of sumatriptan 12 mg, with a maximum of 36 mg in 24 h, reported no increase in adverse events and no medication overuse headache.

Table 2 Drugs used in the acute treatment of cluster headache

Drug	Dosage	Adverse events	Evidence level	Effect
Sumatriptan	6 mg SC	Mild to moderate: Chest symptoms and distal paraesthesia	1B	Effective
	20 mg nasal spray	Mild to moderate: Chest symptoms and distal paraesthesia	1B	Effective
Zolmitriptan	5 or 10 mg nasal spray	Mild: unpleasant taste, somnolence	1B	Effective
Oxygen[a]	100% oxygen 7–12 L/min	None reported	1B	Effective
Lidocaine[b]	Four nasal sprays of 4% lidocaine	Mild: Unpleasant taste	2B	Probably effective
Octreotide	100 µg SC	Mild: GI disturbance, injection site reaction	2B	Probably effective
Dihydroergotamine	1 mg nasal spray	Not reported	2B	Probably ineffective

GI gastrointestinal, *SC* subcutaneous

[a]Demand valve oxygen can be used, which provides flow rates up to 160 L/min

[b]Different dosages and modes of administration have been described. Another option is 0.5–0.8 mL 4% lidocaine using a nasal dropper

Triptan nasal spray is less effective at aborting cluster headache attacks because resorption of the drug through the mucosa is too slow. However, when the patient cannot tolerate injections and the attacks are relatively long (> 1 h), triptan nasal spray can be an alternative treatment. A randomised controlled trial (RCT) in 118 patients who treated 154 attacks [35] found that intranasal sumatriptan 20 mg was superior to placebo in headache relief (57 vs. 26%, respectively; $p = 0.002$) and pain-free rate after 30 min (47 vs. 18%, respectively; $p = 0.004$). This trial advised using one dose of sumatriptan 20 mg in the contralateral nostril because of the concurrent rhinorrhoea, although another trial showed an identical effect regardless of which nostril received the spray [36]. Two RCTs investigated intranasal zolmitriptan. In the first, 69 patients treated three attacks: one with a placebo, one with zolmitriptan nasal spray 5 mg and one with zolmitriptan nasal spray 10 mg. Pain relief was observed in 21%, 40% and 62%, respectively, in the three groups [37]. In the second trial, 52 patients with cluster headache had a significant reduction in pain of, respectively, 50% and 63.3% at 30 min after administration of zolmitriptan nasal spray 5 and 10 mg [38].

The slow-acting mechanism of triptan tablets means they are not considered a viable treatment option, with the exception of frovatriptan, which can be considered in transitional therapy.

3.1.2 High-Flow Oxygen

High-flow oxygen is another valid first-choice treatment to effectively relieve the pain of cluster attacks when used as soon as possible after onset of an attack. The mechanism of effect needs further clarification, but the most likely mechanism is through inhibition of neuronal activation in the trigeminocervical complex and of dural inflammation [39, 40]. The great advantage of oxygen over other acute treatments is the lack of adverse events. Efficacy was proven many years ago, with 75% of patients with cluster headache reporting significant relief in seven of ten cluster attacks using 7 L of high-flow oxygen for 15 min [41]. This effect was further confirmed in two randomised double-blind trials, which reported significant pain reduction in the groups using high-flow oxygen at 7 and 12 L/min for 15 min compared with placebo [42, 43]. Two recent studies suggested a high flow rate (12 L/min) to be more effective than a low flow rate [43, 44]. Subsequent to this suggestion, a novel technique was developed: demand valve oxygen (DVO), which supports a very high flow rate of up to 160 L/min, with flow rate depending on the patient's breathing rate. In this very small study, all four patients achieved pain freedom in an average of 12 min. The most recent study comparing different types of oxygen masks advised the use of DVO over the 'traditional' mask, although results were not significant ($p = 0.119$) in this group of 42 patients. However, patients showed a significant preference for the DVO over a traditional mask ($p < 0.001$) [45].

3.1.3 Lidocaine Nasal Spray

Only four published papers have investigated the use of intranasal lidocaine. An early case series evaluating 4% lidocaine 1 mL administered in the nostril ipsilateral to the pain reported that four patients experienced a ≥ 75% headache reduction within 3 min [46]. In a later trial, 4 of 12 patients responded to 4% lidocaine 0.5–0.8 mL using a nasal dropper [47]. Another open-label trial reported that 54% of patients obtained mild or moderate relief [48] with four sprays of lidocaine 4% in the ipsilateral nostril. In a subsequent crossover trial, all 15 patients with nitroglycerin-induced cluster headache attacks experienced a positive effect with a bilaterally administered intranasal cotton swab previously immersed in 10% lidocaine [49]. Only minor and local side effects were reported. However, since evidence is scarce and administration methods vary, treatment with intranasal lidocaine requires further studies and should only be used if sumatriptan and oxygen are ineffective or contraindicated.

3.1.4 Somatostatin and Somatostatin Analogues

Elevated levels of serum calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) have been found during cluster headache attacks. Somatostatin has been shown to inhibit various neuropeptides, including CGRP and VIP. Furthermore, patients with cluster headache have lower plasma somatostatin levels than healthy controls both during attacks and in attack-free periods [50].

In the 1980s, two small double-blind studies suggested the efficacy of somatostatin [51, 52]. The first study reported significantly reduced maximum pain intensity and duration of pain in 72 attacks in eight patients with intravenous infusion of somatostatin 25 µg/min for 20 min compared with placebo. The second study reported the same effects on maximal pain intensity with subcutaneous somatostatin compared with ergotamine. However, somatostatin was less effective in the reduction of pain duration, probably because of its very short half-life of several minutes [53]. Therefore, using somatostatin as a potential acute treatment for cluster headache seems to require continuous intravenous infusion to maintain a therapeutic plasma level.

A placebo-controlled double-blind crossover study in 57 patients with eCH and cCH shifted its focus to octreotide 100 µg, a somatostatin analogue with a half-life of approximately 1.5 h [53]. This study reported a headache response of 52% compared with 36% with placebo [54]. When comparing the number of responders in this study with the number of responders in the studies of subcutaneous sumatriptan 6 mg, octreotide seems inferior to sumatriptan. However, since octreotide can be used in patients with ischaemic heart disease, it is a viable alternative to oxygen in patients with cluster headache who cannot use triptans. A recent phase

II trial assessing the efficacy and safety of subcutaneous pasireotide (SOM230; 0.9 and 1.5 mg), a somatostatin analogue with a half-life of approximately 12 h, was terminated because of non-efficacy in the first phase [55].

3.1.5 Ergotamine

Ergotamine is one of the oldest agents used in the treatment of cluster headache. However, since it is associated with serious side effects, including myocardial infarction, limb ischaemia and fibrotic changes [56], ergotamine is rarely used in the treatment of cluster headache. An RCT showed that intranasal dihydroergotamine spray was not superior to placebo in the abortion of attacks. However, the intensity of single attacks was significantly lower in patients treated with intranasal dihydroergotamine spray [57].

3.2 Prophylactic Treatment

Current guidelines include various options for prophylactic therapy based upon different levels of evidence. Prophylactic treatment drugs of first choice are verapamil, lithium and topiramate; see Table 3 for a summary.

3.2.1 Verapamil

Verapamil is the drug of first choice in the preventive treatment of cluster headache. Its mechanism of action remains to be elucidated, but current understanding is that verapamil exhibits its effect through CGRP-release modification and possible circadian rhythm modification. Blockade of presynaptic calcium channels prevents CGRP release [58], possibly inhibiting the CGRP-induced hyper-responsive state [59]. Furthermore, calcium channels appear to play a role in the circadian rhythm, which is hypothesised to play a major role in the pathophysiology of cluster headache.

Although verapamil is recognised as a drug of first choice, only five trials (two of which were RCTs) have investigated the prophylactic effect of verapamil in cluster headache. The first open-label study included five patients with cCH who received verapamil 160–720 mg [60]. A subsequent open-label trial in 48 patients with cluster headache (33 eCH, 15 cCH) showed a reduction in headache frequency of more than three-quarters in 69% of patients [61]. The average verapamil dose was 354 mg (range 240–600) in the eCH group and 572 mg (range 120–1200) in the cCH group. The most recent open-label trial showed attack freedom in 94% of patients with eCH (49/52) and in 55% of those with cCH (10/18) with verapamil 200–960 mg [62]. In 1990, a double-blind crossover RCT in 30 patients with cCH compared the effects of verapamil 360 mg daily versus lithium 900 mg daily. Both lithium and verapamil produced significant improvements in headache index (verapamil 50%, lithium 37%) and analgesic consumption (58% in both groups), but headache index was not further specified [63].

The only double-blind randomised placebo-controlled trial studying verapamil (1:1 treatment allocation, verapamil 360 mg vs. placebo) showed a significant decrease in daily attack frequency (0.66 ± 0.88 vs. 1.65 ± 1.01, respectively; $p < 0.001$) and daily analgesic use (0.5 ± 0.87 vs. 1.2 ± 1.03, respectively; $p < 0.004$) in 30 patients with eCH [64].

In current daily practice, patients receive verapamil at a mean dose of 578 mg daily (maximum 1200 mg daily). The dosage must be slowly increased to minimise side effects and to determine the lowest effective dosage. Adverse events mainly include cardiac-related side effects. Two studies have investigated these cardiac side effects. The first reported arrhythmias in 19% (12/108) and bradycardia in 36% (39/108) of patients receiving verapamil up to 960 mg daily [65]. The second study, conducted in patients receiving verapamil ≥ 720 mg daily, reported adverse cardiac events in 38% (11/29) and serious adverse events in 14% (4/29) of patients [66]. In 2016, 22 clinical cardiology experts were interviewed in a Delphi study to formulate guidelines on ECG monitoring during verapamil treatment. They recommended that a pre-treatment ECG always be performed, but no consensus was reached on ECG monitoring during treatment. ECG *before* dose increase was recommended by 50%, whereas 60% recommended an ECG *after* dose increase [67].

3.2.2 Lithium

Lithium is next in line if verapamil fails or if the patient cannot start or continue verapamil treatment. Only three trials have investigated lithium therapy in cluster headache. The only placebo-controlled RCT was negative, but this trial, including 27 patients with eCH, used lithium 800 mg (leading to plasma lithium levels of 0.5–0.6 mmol/L) daily, and the endpoint was set at only 1 week [63, 68]. In a retrospective study of 19 patients, all eight patients with cCH experienced a positive effect in the first 2 weeks of treatment with lithium carbonate (serum concentration 0.7–1.2 mmol/L). Four of the 11 patients with eCH showed a positive effect that could be attributed to the lithium therapy [69]. Another double-blind study compared lithium 900 mg with verapamil 360 mg in the prevention of cCH attacks. Both drugs resulted in improvements in headache index (verapamil 50%, lithium 37%) and analgesic consumption (58% in both groups), but a shorter latency period and fewer side effects were observed in the verapamil group [63]. These latter two studies suggested the placebo-controlled trial used an insufficient dosage and that the endpoint was set too early. Furthermore, studies suggest that lithium

Table 3 Drugs used in the prophylactic treatment of cluster headache

Drug	Dosage	Adverse events	Evidence level	Effect	Clinical notes[a]
Verapamil	≤ 960 mg QD	Mild to moderate: Constipation, arrhythmia, fatigue, bradycardia. No SAEs reported with a daily dose < 720 mg	1B	Effective	First-choice treatment for eCH and cCH. ECG monitoring mandatory for conduction times
Lithium	Serum concentration 0.7–1.2 mmol/L	Moderate to severe: Nausea, dizziness, tremor, polyuria	2B	Effective	Not suitable in the treatment of short bouts in eCH. Frequent serum concentration and mandatory thyroid and kidney function monitoring
Topiramate	≤ 200 mg QD (one trial described dosages of ≤ 400 mg daily)	Mild to moderate: Paraesthesias, depression, drowsiness, speech disturbances, dizziness, altered taste. Otherwise good tolerability in lower range of doses (< 100 mg/day)	2B	Probably effective	Monitor mood changes. Can be used in the treatment of eCH and cCH
Galcanezumab	300 mg SC monthly	Mild to moderate, injection site pain	2	Probably effective in eCH	Promising option in the treatment of eCH. Not proven in cCH
Warfarin	INR 1.5–1.9	Mild: Epistaxis, skin bruises	2B	Inconclusive	
Melatonin	10 mg QD	None reported	2B	Inconclusive	
Methysergide	≤ 6 mg QD	Mild to severe: dizziness, nausea, peripheral arterial insufficiency, peripheral oedema. Chronic use can cause retroperitoneal fibrosis	4	Probably effective	No longer available
Psilocybin	Sub-hallucinogenic doses	None reported	4	Inconclusive	
Sodium oxybate	1.5–8.5 g/night	Mild to moderate: dizziness, weight loss, difficulty waking up	4	Inconclusive	
Fremanezumab	Unknown	Unknown	RCT halted	Probably not effective	

cCH chronic cluster headache, *ECG* electrocardiogram, *eCH* episodic cluster headache, *INR* international normalized ratio, *QD* daily, *RCT* randomised controlled trial, *SAE* serious adverse event, *SC* subcutaneous

[a]Clinical notes are based on authors' expert opinions

therapy is more effective in cCH than in eCH, but more studies are needed to confirm this suggestion.

Despite the positive therapeutic effects with lithium, side effects can lead to discontinuation of therapy. Nausea, dizziness and tremor are among the many side effects of lithium, and long-term use can cause kidney dysfunction and provoke hypothyroidism. To minimise the negative side effects and monitor possible toxic effects, serum concentrations and liver, thyroid and kidney function should be checked regularly during treatment.

3.2.3 Topiramate

Topiramate is an alternative preventive therapy in cluster headache, but evidence on its effect is scarce. The first report on the efficacy of topiramate was a case series in which nine of ten patients achieved remission within 3 weeks (dose range 50–125 mg daily) [70]. Similar numbers were reported in the retrospective trial (9 of 12 patients showed significant improvement) [71]. A subsequent prospective open-label trial confirmed these results: 6 of 12 patients with eCH and 9 of 14 with cCH achieved remission with a mean dose of 100 mg daily (range 25–200) [72]. The most recent trial was a prospective open-label trial in which 9 of 12 patients with eCH showed remission. In this study, a very high (start) dosage of topiramate was used, with a mean dosage of 273 mg (range 100–400). Two patients experienced side effects that led to treatment discontinuation [73]. One open-label trial showed no significant improvement in 33 patients who received various dosages up to 250 mg daily. Daily attack frequency was reduced by > 50% in only seven patients. In this trial, 22 patients did not achieve a dosage higher than 100 mg because of side effects [74]. In daily practice, topiramate is used in both patients with eCH and those with cCH but should only be used if treatment with verapamil or lithium has failed. The dosage should be titrated slowly to manage side effects since they are frequent and include paraesthesia, mood swings and speech disturbances.

3.2.4 Melatonin

A remarkable clinical feature of cluster headache attacks is their tendency to occur in a specific circadian rhythm. This suggests hypothalamic involvement in the pathophysiology and supports the use of melatonin as a therapeutic agent in cluster headache. However, evidence is mixed. A small RCT in 20 patients showed a significant reduction in headache frequency in five of ten patients receiving melatonin 10 mg compared with placebo ($p < 0.001$). No attack reduction was found in patients with cCH ($n = 2$) [75]. Some response to melatonin in two patients with cCH was shown in a case series [76]. A study in nine patients (six eCH and three cCH) showed no additional therapeutic effect from the addition of melatonin to their usual treatment [77].

3.2.5 Sodium Valproate

In an early open-label trial, sodium valproate (600–2000 mg) was effective in the treatment of cluster headache in 11 of 15 patients: nine patients achieved complete remission and two showed a partial effect [78]. A later double-blind placebo-controlled RCT in 50 patients (37 eCH, 11 cCH, two unspecified) showed no difference between the sodium valproate group and placebo, with a 50% decrease in attack frequency in 50% of those receiving sodium valproate and in 62% of those receiving placebo. The authors stated that the 62% placebo response was probably because of spontaneous cessation of the cluster episode in patients with eCH. However, a subgroup analysis showed no difference in response in patients with cCH [79]. Evidence is insufficient to evaluate the efficacy of sodium valproate in the prophylactic treatment of cluster headache.

3.2.6 Clomiphene

The hypothalamus is involved in cluster headache pathogenesis. Hormonal manipulation is one method of altering hypothalamic function. Testosterone could be a viable target since diminished testosterone levels have been shown in patients with cluster headache [80]. Clomiphene is a non-steroidal agent that actively blocks hypothalamic oestrogen receptors, thereby inhibiting gonadotropin-releasing hormone secretion. This increases the concentration of luteinising hormone and follicle-stimulating hormone, which in turn stimulates the testes and ovaries to produce androgens and oestrogen.

Two case reports highlighted the possible efficacy of clomiphene in the treatment of cluster headache [81, 82]. These reports resulted in a prospective open-label trial in seven patients with cCH and eight with eCH. The average time between start of clomiphene and the resolution of pain was 15 days, and time to remission was 60 days. The authors concluded that clomiphene was effective and could revert cCH into eCH. Furthermore, in contrast with traditional testosterone-replacement therapy, clomiphene does not interact with spermatogenesis [83]. Hormonal manipulation in cluster headache is an interesting treatment method, but further studies regarding this subject are needed.

3.2.7 Methysergide

Methysergide is an effective treatment for cluster headache, although evidence for this efficacy is scarce. An important aspect of this treatment is the risk of retroperitoneal fibrosis

after long-term use, which led to a recommendation that treatment not be continued for longer than 4–6 months. Unfortunately, the compound is no longer available. A survey among members of the International Headache Society showed that a vast majority would prescribe the drug to a specific group of patients if it were available [84].

3.3 Transitional Treatment

Since preventive drugs need time to take effect and to be titrated to the therapeutic dosage, transitional treatment has an important place in cluster headache. These transitional treatments generally exert their effect for several weeks to months (see Table 4 for a summary of drugs used in transitional treatment).

3.3.1 Prednisolone

Corticosteroids lower plasma concentrations of CGRP and increase nocturnal melatonin excretion in patients with cluster headache [85]. However, the exact mechanism of action of prednisolone in cluster headache is unknown. Although placebo-controlled trials are lacking, high doses of corticosteroids are highly effective in the treatment of cluster headache, as described in four open-label trials [86–89] and one case series [90]. There is no consensus on mode of administration (intravenous vs. oral), dosage or duration. In the most recent retrospective study, intravenous methylprednisolone was administered in dosages ranging from 500 mg for 5 days to 1 g for 9 days, with and without oral tapering of prednisone. In this study, all patients responded to treatment, with 32 patients (86.5%) achieving attack freedom [88]. Since chronic use of corticosteroids is associated with potentially serious adverse events, only short-term use is recommended. Since the studies all used different administration routes (intravenous vs. oral), dosages and tapering, no single recommendation regarding dosage can be made. We therefore advise starting with a high dose and gradually tapering down. Our clinical experience is that attacks often return when corticosteroids are reduced to < 30 mg per day. We suggest tapering more gradually in patients with eCH or cCH experiencing long bouts. No significant side effects have been described with short-term use.

3.3.2 Greater Occipital Nerve Injection

In recent years, evidence has emerged that local steroid injection of the greater occipital nerve (GON) may have prophylactic efficacy in cluster headache [91–97]. This therapeutic intervention for the treatment of chronic local neuropathic pain has existed since the 1960s, with effectiveness in cluster headaches being reported as early as 1985 in 12 patients with eCH and eight patients with cCH [98]. Subsequent prospective studies [93, 99] and two larger retrospective case series [91, 92] confirmed these initial results, suggesting an important role for GON injection in the transitional therapy of cluster headache. Evidence indicates GON injection has a greater effect in eCH than in cCH [92, 99]. The first randomised placebo-controlled double-blind trial showed compelling evidence in favour of GON injection, with 85% (11/13) of patients achieving attack freedom in the first week compared with none of ten patients in the placebo group ($p = 0.0001$). Furthermore, eight patients remained attack free for the subsequent 4-week period [94]. A second larger RCT showed two or fewer daily headache attacks in the injection group in 20 of 21 patients compared

Table 4 Drugs used in the transitional treatment of cluster headache

Drug	Dosage	Adverse events	Evidence level	Effect	Clinical notes[a]
GON injection	Single injection[b]	Mild: Local discomfort	1B	Effective	Promising option in the treatment of eCH. Insufficient data regarding chronic use
Prednisolone	Inconclusive. 60-mg tablet daily start dose, taper every 5 days with 5 mg[c]	Increased serum glucose	4	Probably effective	Can be highly effective, but only suitable for short-term transitional treatment
Dihydroergotamine	IV regimen	Mild to moderate: Nausea, leg cramp, diarrhoea	4	Probably effective	
Frovatriptan	2.5 mg tablet QD or BID	Dizziness, fatigue, nausea	Level 4	Inconclusive	

BID twice daily, *eCH* episodic cluster headache, *GON* greater occipital nerve, *IV* intravenous, *QD* once daily

[a]Clinical notes are based on authors' expert opinions

[b]Different corticosteroids can be used with or without addition of a local anaesthetic

[c]Different tapering can be used according to cluster headache type. It is recommended to taper faster in eCH with short-lasting cluster bouts

with 12 of 22 controls ($p = 0.012$) for the first 15 days after injection [96]. However, these trials were hampered by the heterogeneity of the patients with eCH and cCH and ongoing prophylactic treatment. Nonetheless, GON injection has been shown to be well-tolerated, with only minor local side effects described. An ongoing double-blind RCT is studying the efficacy of GON infiltration with steroids as first-choice treatment in eCH [100].

3.3.3 Frovatriptan

A case series on oral frovatriptan 2.5 and 5 mg reported attack freedom in eight of nine patients with eCH, with the ninth patient exhibiting a 50% response in attacks. Of eight patients with cCH, three experienced 100% response, one experienced a 75% reduction, two experienced a 50% reduction and two experienced no improvement [101]. Only one randomised double-blind controlled trial has studied frovatriptan, but this trial was cancelled because of enrolment problems [102].

3.3.4 Dihydroergotamine

Intravenous dihydroergotamine is effective when administered for a minimum of 3 consecutive days [103]. Success rates of 57–100% were reported in four open-label studies [104–107]. In contrast to the possibly severe side effects of ergotamine, the most common adverse events experienced with intravenous dihydroergotamine were nausea (58%) and leg cramp (28%). The drug was otherwise well-tolerated [107].

3.4 Evolving Therapies

3.4.1 Monoclonal Antibodies Targeting Calcitonin Gene-Related Peptide

In recent years, signalling molecule CGRP has gained considerable attention in the treatment of migraine. In cluster headache, serum CGRP levels are elevated during both spontaneous and nitroglycerine infusion-induced cluster headache attacks [108–110] and during active-phase cluster headache compared with patients during remission. Furthermore, a recent study showed that CGRP can induce cluster headache attacks [111]. However, in that study, attacks were only provoked in 'in-bout' episodic cluster headache and active-phase cCH, suggesting an alternating susceptibility of the brain to cluster headache attacks. This combined evidence suggests a possible efficacy of CGRP antagonism in cluster headache treatment.

TEV-48125 (fremanezumab) and LY2951742 (galcanezumab) have been studied in the prophylactic treatment of eCH. In the 8-week double-blind placebo-controlled treatment period, subjects treated with galcanezumab showed a mean change of − 8.7 attacks per week (from 17.8 to 9.1 attacks per week) compared with a change of − 5.2 attacks per week (from 17.3 to 12.1 attacks per week) for subjects receiving placebo (galcanezumab vs. placebo; $p = 0.036$) [112]. Adverse events were similar between groups, except that 8% of those receiving galcanezumab reported injection site pain. This first study shows the efficacy of galcanezumab in the treatment of eCH, but longer studies are necessary to determine the (long-term) safety and durability of this drug. As of June 2019, galcanezumab has been approved in the USA for the treatment of eCH [113]. Since no long-term studies have been conducted, treatment should be discontinued when patients are out of cycle to lower the chances of developing neutralising antibodies.

The fremanezumab trial was halted in June 2019 because futility analysis revealed that the primary endpoint (mean change from baseline in the weekly average number of cluster headache attacks during the 4-week treatment period) was unlikely to be met [114]. Furthermore, studies comparing the efficacy and safety of both drugs in the prevention of cCH were terminated because futility analysis revealed that the primary endpoint was unlikely to be met [115, 116].

3.4.2 Sodium Oxybate

Sodium oxybate has been investigated as a prophylactic drug in one case report [117] and one small open-label study in four patients [118]. The latter study showed a long-lasting improvement (mean 19 months in three patients, 8 months in one patient) in frequency and intensity of both nocturnal and daytime headaches. Furthermore, response to sodium oxybate appeared to be dose dependent, suggesting a 'true' effect.

3.4.3 Psilocybin and Lysergic Acid Diethylamide (LSD)

A higher prevalence of illicit drug use has been reported in people with cluster headache compared with the general population [119–121], with a high percentage of patients believing that these drugs have preventive efficacy. However, scientific evidence for its effect on cluster headache is lacking.

Efficacy of the 'cluster busters' psilocybin-containing mushrooms and lysergic acid diethylamide (LSD) has not yet been well-documented. One case series of 53 individuals showed promising results [122] for LSD as a prophylactic drug and for psilocybin as both a prophylactic and an acute treatment. However, this study had considerable limitations, including possible recall and selection biases and an open-label, retrospective study design. The safety and efficacy of oral psilocybin as a transitional treatment is being studied in

cluster headache using a double-blind randomised crossover design [123].

3.4.4 Other Drugs

Other drugs are currently being studied as attack treatments. A phase II trial is investigating intranasal ketamine hydrochloride in an open-label proof-of-concept study [124], and a double-blind, placebo-controlled trial is investigating zolmitriptan 1.9 mg patch [125].

All drugs currently prescribed for the treatment of cluster headache are used off-label, as they are developed for other indications. As cluster headache has a high disease burden, medication with a low level of evidence must be tried in daily practice. We have described the most promising drugs and those with the most evidence. In addition to the drugs mentioned, some currently available drugs are also described in open-label studies, case series and expert opinion articles, including baclofen, indomethacin, pizotifen and testosterone-replacement therapy.

4 Conclusion and Clinical Recommendation

Treatment of cluster headache entails a combination of fast-acting abortive treatment, transitional treatment and preventive treatment. A plethora of pharmacological treatment options is available and has been described in the literature. Unfortunately, very few pharmacological treatment options have a high level of evidence.

When treating patients with cluster headache, it is important to first start abortive treatment. First-choice abortive treatments include high-flow oxygen and/or subcutaneous sumatriptan. Other options can be used only if these are ineffective or contraindicated. Prophylactic therapy is necessary for patients with cCH or for patients with eCH in an active cluster episode. In patients with eCH, the type of prophylactic treatment depends on bout length, because titrating to an adequate dosage of prophylactic drug can take weeks. In this period, transitional therapy can also be considered. The primary goal of prophylactic therapy is attack freedom. The first-choice prophylactic therapy is verapamil, followed by lithium and topiramate. If adequate treatment with at least three drugs that showed efficacy over placebo has failed, the condition is defined as refractory cCH according to the consensus reached by the European Headache Federation in 2014 [126]. Other pharmacological therapies can be tried in a trial-and-error approach only if patients present with refractory cCH. However, since the evidence level is low, we recommend also considering one of several neuromodulatory options. When patients are in a sustained period of attack freedom, prophylactic therapy can be tapered. Since effective preventive treatment can take several weeks to titrate, transitional treatment can be of great importance in the treatment of cluster headache. At present, GON injection is the most proven transitional treatment. Other options are high-dose prednisone or frovatriptan. Our clinical recommendations are summarised in Table 5.

Cluster headache therapy needs to be highly individualised, especially in patients with cCH since attack freedom cannot always be achieved. Sometimes, the best effect/side effect ratio needs to be titrated in close collaboration with the patient.

Table 5 Clinical recommendations

Acute treatment	SC sumatriptan 6 mg and/or
	High-flow oxygen 9–12 L/min for 15 min[a]
Prophylactic treatment	
First-choice treatment	Verapamil up to 720–960 mg daily
	Lithium (serum concentration 0.7–1.2 mmol/L in cCH and long eCH episode)
	Topiramate up to 200 mg daily
Second-choice treatment	No clear recommendation can be given due to low evidence level of other pharmacological treatment options. We recommend considering one of several neuromodulatory options in refractory cCH
Transitional treatment	GON injection ipsilateral to the pain
	Prednisolone (different dosages available)
	Frovatriptan 2.5–5 mg daily

cCH chronic cluster headache, *eCH* episodic cluster headache, *GON* greater occipital nerve, *SC* subcutaneous

[a]If available, demand valve oxygen can be used, which provides flow rates up to 160 L/min

Compliance with Ethical Standards

Conflict of interest MDF has received consultancy fees from Medtronic, Salvia, Novartis, Amgen, Lilly and TEVA. RF has carried out advisory work for Lilly, TEVA and Allergan and received lecture fees from Novartis. JH has carried out advisory work for Lilly. RBB and PGGD have no conflicts of interest that are directly relevant to the content of this article.

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