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PROF. LUC ZIMMER (Orcid ID : 0000-0002-2805-7098)

DR. SOPHIE LANCELOT (Orcid ID : 0000-0002-3637-8035)

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Cluster headache:

State of the art of pharmacological treatments, and therapeutic perspectives

Running head: Treatments and perspectives in cluster headache

Pierre **Courault**^{a,b}, Geneviève **Demarquay**^b, Luc **Zimmer**^{a,b,c,d}, Sophie **Lancelot**^{a,b,c,*}

^aLyon Neuroscience Research Center (CRNL), Université de Lyon, CNRS, INSERM, Lyon, France

^bHospices Civils de Lyon (HCL), Lyon, France

^cCERMEP-Imaging platform, Groupement Hospitalier Est, Bron, France

^dNational Institute for Nuclear Science and Technology (INSTN), CEA, Saclay, France

***Corresponding author:**

Sophie **Lancelot**

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Université de Lyon Ringgold standard institution - Centre de Recherche en Neurosciences de
Lyon, Lyon, Auvergne-Rhône-Alpes, France

sophie.lancelot@univ-lyon1.fr

Accepted Article

ABSTRACT

Cluster headache (CH) is the most common form of trigeminal autonomic cephalalgia. Current treatments have several limitations and new drugs are required. This article first briefly reviews present acute and preventive treatments in CH, their mechanism of action and limitations, then describes the state of the art in recent clinical drug trials since 2015, and ends with a critique of trials in the CH field.

Research is limited by lack knowledge of pathophysiology, lack of animal models. In the past 5 years, no brand-new treatment has emerged, but promising drugs, such as CGRP(R) antibodies, are under study. According to the literature and guidelines, clinicians and researchers should be aware of many limitations in study protocols: concomitant medication, patient sample size, patients' protocol compliance, and study designs that tend to restrict patient recruitment.

Keywords: Cluster headache

INTRODUCTION: EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Cluster headache (CH), also known as “suicide headache”, belongs to the primary headache family and trigeminal autonomic cephalalgia (TAC) sub-family. Attacks are characterized by severe to very severe strictly unilateral orbital, supra-orbital and/or temporal pain lasting 15 to 180 minutes [1]. Pain is associated with a typical clinical picture combining signs ipsilateral to the headache: conjunctival injection, lacrimation, rhinorrhea, eyelid edema, sweating, and miosis or ptosis with a sense of restlessness. Patients experiencing such attacks at a frequency between one every other day and eight per day are diagnosed as having CH.

Fifteen percent of these patients are classified as chronic CH (cCH) and 85% as episodic CH (eCH). In eCH, attacks occur in series lasting a week or months, separated by remission periods lasting months or years, while cCH patients have no remission periods. Prevalence is around 1 per 1,000 and mainly affects men, with an M:F sex ratio of 4.3 [2]. CH is diagnosed in young adults between 20 to 40 years, with a mean age at onset of 30 years [3]. Genetics suggests higher risk for first and second-degree family members. Twin studies suggested a role of genetics but also the importance of environmental factors [4]. Risk factors and comorbidities include trauma [5] and smoking, illicit drugs and alcohol [6, 7].

The pathophysiology of CH remains unclear, but peripheral and central mechanisms involving three important systems may be entangled: the trigeminovascular system, parasympathetic system and hypothalamus [8]. Peripherally, activation of trigeminovascular afferences on cranial vessels and dura matter can transmit nociceptive input and release neuropeptides [9]. Trigeminal ganglion neurons then relay information to higher structures through the trigeminocervical complex (TCC). Here, the parasympathetic system, through the superior salivatory nucleus, activates the sphenopalatine ganglion, completing the trigeminal autonomic arc reflex. This entire trigeminal autonomic arc reflex is responsible for vasoactive modulation and release of many neuropeptides, such as Calcitonin Gene-Related Peptide (CGRP), neuropeptide Y, vasoactive intestinal polypeptide or pituitary adenylate cyclase-activating peptide, involved in vasodilatation and in pain processes [10, 11]. Parasympathetic nerves fibers are responsible for a part of the clinical parasympathetic symptoms described above. Centrally, fMRI and PET studies suggested that the hypothalamus plays a central role in CH [12–15]. By its multiple connections, it is thought to

trigger CH attacks and/or regulate pain processes. The periodicity of CH episodes in eCH suggests a relation with circadian and seasonal rhythms, also controlled by the hypothalamus through melatonin and orexin secretion [16, 17].

Hypotheses involving other neurotransmitter systems have also been put forward. In the glutamatergic field, reduced levels of kynurenine metabolites suggest a hypothesis of over-activation of N-methyl-D-aspartate (NMDA) receptors in CH [18].

The pathophysiology of CH is still unknown and very complex to elucidate. Unfortunately, lack of knowledge of the precise mechanisms of CH leads to therapeutic deadlock. Patient associations are strongly advocating new clinical studies in this pathology. The purpose of the present review is to present a brief update on CH treatments and their limitations, a state of the art on clinical drug trials since 2015, and a critique of trials in the CH field.

CURRENT TREATMENTS AND THEIR LIMITATIONS

According to French and United States guidelines [19, 20], CH treatments comprise three different groups: acute, preventive and transitional. Drugs used in acute treatment are effective in aborting CH attacks and reducing severity; drugs used for prevention aim to reduce the frequency of CH attacks; and drugs used as transitional treatment are employed at the onset of a cluster period. Table I summarizes the most important treatments in each group, with their mechanisms and their limitations.

a. Acute treatments

Sumatriptan

Sumatriptan administered subcutaneously at 6 mg is effective for relieving attacks in eCH and cCH and is the first-line acute treatment. Pain relief is achieved in 15 minutes for 75% of the patients [21]. Its efficacy is proved by two level I randomized controlled trials with level A recommendation [21, 22]. Sumatriptan is usually well tolerated, with only non-serious adverse events such as injection site reaction, nausea and vomiting, dizziness, fatigue or paresthesia.

Sumatriptan is an agonist of 5-hydroxy-triptamine-1 (5-HT₁) and more precisely 5-HT_{1B/1D} and to lesser extent of 5-HT_{1A} and 5-HT_{1F}, without any effects on other 5-HT families [23–25]. It has

three putative levels of action: cranial vessels, inhibition of peripheral trigeminal afferents, and second-order neurons of trigeminal-cervical complex. Vascular 5-HT_{1D} was first suggested as being implicated, by a vasoconstrictive effect as in migraine [26], but this has been questioned and may not be the only explanation [27, 28]. Animal studies showed peripherally, inhibition of trigeminal afferents reduces neurogenic inflammation by blocking plasma protein extravasation [29], reducing the release of neuropeptides such as CGRP involved in pain processes [30] and inducing vasomotor changes in dural vessels [31]. Sumatriptan can also inhibit neurotransmission in second-order neurons of the TCC [32]. These mechanisms might implicate the 5-HT_{1B/1D} receptor or 5-HT_{1F} receptor [33]. A more central CNS effect is controversial. Sumatriptan is a hydrophilic triptan which has difficulty to cross the blood-brain barrier (BBB). Studies suggest that disruption of the BBB is needed for sumatriptan to exert a central effect [34, 35].

Although sumatriptan is considered as first-line acute CH treatment, it also has limitations. Firstly, not all patients respond: around 25% are resistant [21, 22]. Furthermore, not all patients are eligible for sumatriptan treatment, due to important contraindications: i.e., cardiovascular or cerebrovascular disease.

High-flow oxygen

High-flow oxygen is the second most effective acute treatment for CH attacks. Oxygen therapy has been known since the 1950s [43]. For years, studies tried to determine suitable flow in CH treatment, starting with 7 L/min and going up to 15 L/min, with different administration devices [44–48]. In these studies, high-flow oxygen relieved pain in approximately 80% of patients within 6 to 15 minutes, with few adverse events. The most recent guidelines, with level A recommendation, advocated high-flow oxygen therapy at 12-15 L/min for 15-20 minutes via a high-concentration mask [19, 20]. Hyperbaric therapy was also studied, but seemed not to be effective and is not recommended [49].

The precise action mechanism of oxygen for pain relief in CH remains unclear. Hypotheses include inhibition of parasympathetic activity in the TCC [50], reduction of inflammation by inhibition of neurogenic plasma protein extravasation in the dura matter [51], or a direct vasoconstrictive effect of oxygen on cerebral vessels [52].

A large observational study showed that eCH patients responded better and faster than cCH patients to inhaled oxygen [44]. In the *Kudrow 1981* study, 25% of patients underwent a rebound

effect, synonymous with therapeutic failure. However, these negative results tend to be attenuated in clinical practice [53] due to improvement in techniques and use of higher flow, for example with demand-valve oxygen [48]. Other limitations concern rules for the safe use of oxygen and devices: patients have to be independent in their use of the device and thus need to be educated, otherwise of efficiency is impaired [19, 54]. The cost of devices and of oxygen also raises questions of equal accessibility; some patients reported using welding grade oxygen, cheaper than medical oxygen, but likely less safe [54].

b. Preventive treatments

Verapamil

Based on the vascular hypothesis of headache pathophysiology, calcium antagonists such as verapamil were proposed in the 1980s for migraine and by extension for CH [55, 56]. Two studies (one class II and one class III randomized controlled trial) subsequently demonstrated the efficacy of verapamil in CH [57, 58]. Different protocols were described, with dose increments of 80 mg every 10 to 14 days, or more quickly with 120 mg every 2 days [59–61]. Verapamil is now prescribed off-label for prophylaxis of CH. Depending on guidelines, it may be recommended in first-line, with different levels of recommendation [19, 20, 62], with gradual augmentation to attempt 360 or 480 mg/day in three fractions. High-dose prescriptions up to 1,200 mg have also been described [56].

The mechanism of action of verapamil in CH is also unclear. A vasoconstrictive effect was the first hypothesis, as described in migraine, but the need for higher doses and the different pathophysiology of CH suggest another mechanism might be implicated [56], such as inhibition of CGRP release by blockage of voltage-dependent calcium channels in presynaptic dura neurons [63]. Given the circadian rhythm of CH, verapamil might also exert its effect by modulating this rhythm [64].

The main limitation of verapamil is its cardiac effects. Guidelines recommend electrocardiogram before treatment initiation and then careful monitoring [60]. Although clinical randomized studies showed non-serious adverse events in CH, cardiac adverse events should not be underestimated [65], and may be more frequent in clinical practice than in clinical trials due to the high doses prescribed [66]. Moreover, verapamil is known to be metabolized and to be an inhibitor of

cytochrome P450 3A4 and P-glycoprotein transporter [67]. Interactions with other drugs with cardiologic effects might also exacerbate cardiologic risk: for example, associating verapamil and lithium, both used in CH, is not recommended. Prescribers need to be aware of potential drug-drug interaction with verapamil [68]. As previously outlined, verapamil should be started gradually, to avoid cardiologic adverse events; however, regarding time to effective dose, patients are sometimes unfortunately left for a period of latency without any pharmacological effects to prevent CH attacks. Finally, verapamil was also shown to be less effective in cCH than in eCH [69].

Lithium

The first patients treated with lithium in 1974, by Ekblom, had cCH. Then, several series of patients were described in a retrospective study [70]. There are now 2 class II randomized studies of lithium in CH, one versus placebo [71] one versus verapamil [57]. Interestingly, the placebo-controlled study did not show superiority for the primary endpoint. However, this endpoint was only set after 1 week of treatment and the study reported non-significant subjective improvement, suggesting a possible pharmacological effect. Depending on the guidelines, lithium is recommended off-label to reduce attack frequency in CH with different levels of recommendation [19, 20].

The mechanism of action of lithium in CH remains undetermined. Animal studies showed lithium could interfere with monoamine and electrolyte metabolism in the brain [72–74]. More precisely, lithium modulates hypothalamus serotonin release, reported to be implicated in CH pathogenesis [75]. Another mechanism involves modification of the pattern of rapid eye-movement sleep [76], which is disturbed in CH patients [77]. Modulation of opioid receptor affinity could also be involved [78].

Due to its narrow therapeutic window, lithium requires specific follow-up, which could be restrictive for prescribers. Dosage needs to be adapted to the clinical situation, and lithium serum assay is needed to prevent overdose [79]. The therapeutic concentration should not exceed 1.2 mEq/L. Adverse events have been widely reported in patients receiving long-course lithium, and notably kidney and thyroid dysfunction [80]. For these reason, a check-up before initiating the treatment is warranted, with regular follow-up during the course of treatment [19]. Several drug-drug interactions which could lead to overdose are also reported with lithium. Patients need to be

very wary of interactions with over-the-counter drugs such non-steroid anti-inflammatory drugs [81]. Lithium was also shown to be less effective in eCH than cCH patients [82]. Finally, lithium should be prescribed in second-line, after verapamil, which Bussone et al. demonstrated has shorter latency and fewer adverse events [57].

Topiramate

Anticonvulsants have been widely described in pain management and, more recently, topiramate in CH. The first report in 1999 by Wheeler et al. demonstrated efficacy in 10 patients [83], followed by 3 open-label studies [84–86] and 1 retrospective study [87]. In those studies titrations and dosages differed between protocols. Starting doses ranged from 25 to 100 mg daily, titrated every 3 to 7 days for a maximum of 200 mg to 400 mg daily. Three of the 4 studies showed promising results for topiramate in CH [83, 85, 87].

Several action mechanisms have been suggested for topiramate [88]: increased GABA activity, inhibition of voltage-gated sodium/calcium channels, or inhibition of glutamate-mediated neurotransmission.

Due to mixed results and differences in study protocols, no consensus had been reached in guidelines. However, topiramate clearly needs to be started slowly, with titration and adaptation to the clinical situation, and should be resorted to only after therapeutic failure of verapamil and lithium [19, 20]. Leone et al. showed that therapeutic dosage is difficult to achieve due to the absence of dose-effect correlation. Patients have also been reported to abort treatment due to lack of efficacy or to adverse events [85, 86], notably depression, paresthesia, slowed speech and dizziness. Plus, topiramate and lithium have teratogenic effect to be taken into account [89, 90]. Further powerful double-blind placebo-controlled studies are warranted to assess efficacy.

c. Transitional treatments

As mentioned above, transitional treatment is used at the onset of a CH episode to ensure rapid cessation or reduction in the frequency of attacks for a short period of time until a long-term prophylactic agent can take effect. It can therefore be considered as transient prophylaxis. Corticosteroids are the main molecules in this therapeutic class.

Two administration routes are possible for transitional therapy with corticosteroids: oral and injection to the greater occipital nerve (GON).

Three studies assessed oral prednisone in prophylaxis of CH [91–93]. Results showed efficacy for 10 days with doses from 10 to 80 mg/day, with better efficacy with doses >30 mg daily. Recurrence of attacks was reported in all studies. Guidelines for oral prednisolone are inconsistent, with recommendation levels C or U [19, 20]. It is believed that oral corticosteroids act in CH by reducing plasma CGRP levels and increasing melatonin release [94].

Injection of corticosteroids to the GON was reported to have a prophylactic effect. Two level I studies with injection to the GON ipsilateral to the CH showed promising results in rapidly reducing CH attack frequency [95, 96]. The mechanism of action of GON injection remains unclear, but may involve an anesthetic action by reducing nociceptive transmission peripherally and centrally [97].

The main limitations of corticosteroids are their transitional effect and the need for combination with prophylactic drugs. Corticosteroids cannot be used in prophylaxis due to their well-known adverse events in the long term [98]. Again, many administration routes and many protocols are available, with no consensus. More clinical trials are required to determine protocols, number of doses and dosages. One phase 4 study is currently ongoing to investigate the efficacy of GON injection as first-line prophylactic treatment [99].

STATE OF ONGOING CLINICAL TRIALS

a. Method

The flowchart in Figure 1 shows the methods applied in ongoing clinical trials, and Table II shows results for each drug. Bibliographic research for each molecule used in a clinical trial revealed trial structure, state of progress, pharmacological action mechanisms warranting use, and limitations and prospects.

b. Emerging drugs in eCH

1) *Civamide (zucapsaicin)*

What clinical trials?

One clinical trial is ongoing but not recruiting. This phase 3 study's main objective is to evaluate the safety and efficacy of intranasal civamide (zucapsaicin) solution 0.01% for the prevention of attacks during an episodic period. It is a double-blind randomized vehicle-controlled parallel-group multicenter study. Civamide is administered at 20 µg/dose in 0.1 mL vehicle to each nostril, twice a day for 7 days. The main outcome is percentage change in number of cluster headaches per week from baseline to weeks 1 through 3 of the post-treatment observation period. No results have yet been posted. The promoter aims to enroll 180 participants and to complete the study in February 2024.

What evidence for what mechanism of action?

Civamide is a synthetic *cis* isomer of capsaicin, also called zucapsaicin. Capsaicin was first studied in eCH and seems to be effective [100], but civamide showed greater efficacy [101, 102] and safety [103] than capsaicin [104]. Zucapsaicin is a transient receptor vanilloid potential type 1 (TRPV1) modulator and a neuronal calcium-channel blocker [105], causing depletion of type-C nociceptive fibers by initially releasing neurotransmitters, including CGRP and substance P, and then depleting neuron neurotransmitter content [106]. Intranasal application to the trigeminal plexus decreases vasodilation, plasma extravasation and release of histamine/serotonin neurotransmitters, alleviating CH pain. Saper et al. first studied this treatment in eCH patients in 2002 [107] in a multicenter double-blind randomized vehicle-controlled study. Twenty-eight patients were randomized (2:1) to receive civamide or vehicle control for 7 days, at 0.025% in 100 µL, once a day in each nostril, and were monitored for 20 days. Eighteen patients received ≥ 3 days' civamide and ten were in the placebo arm. The civamide group showed a significant decrease in number of headaches from baseline to days 1 through 7 (p-value = 0.03) and trends during days 8 through 14 (p-value = 0.07) and days 15 through 20 (p-value = 0.07). Statistical tests did not show significant intergroup differences for number of severe headaches, pain intensity, associated symptoms or requirement of abortive drugs. Concerning safety, most subjects in the civamide arm had ≥ 1 adverse event, but no serious adverse events were reported. The most common adverse events were nasal burning and lacrimation. These promising results encouraged further studies with larger groups and a less concentrated solution to reduce adverse events.

Unfortunately, in a larger non-published study of 112 patients, civamide decreased the number of CH attacks but failed to show significant results versus placebo [106].

What limitations and prospects?

Due to divergent results, interest in civamide in eCH decreased. Interestingly, a meta-analysis of the two studies cited above showed significant results 3 weeks after treatment compared to baseline (p-value = 0.0312). The FDA ruled that a robustly positive phase III study would be the final clinical study necessary for approval of Civanex®, a civamide-based drug, for prevention of eCH [106]. Thus, the ongoing phase III clinical study is under the spotlight.

2) Nasal Carbon Dioxide

What clinical trials?

One phase II clinical trial assessing nasal carbon dioxide (CO₂) in CH has terminated [108]. Patients had eCH patients with an attack-free remission period lasting at least 1 month within the previous year and were stable on medication. The design was a single group assignment, open-label. Patients received 0.17 L CO₂ delivered through two 10-second administrations in each nostril, up to 6 times, to treat one attack (total, 1.0 L CO₂). Patients could treat up to 3 cluster headache attacks during the treatment phase of the study. The primary outcome was greatest change in headache pain intensity immediately preceding treatment versus 30 minutes post-treatment assessed on a numeric rating scale (NRS). The study was terminated in August 2018 and enrolled 10 participants for a total of 23 attacks. The drugs provided a mean 0.826 (range, -3 to 1) decrease in unit pain intensity. No serious adverse events were reported, but 5 adverse events occurred (goiter, lacrimation increase, vomiting, CH, headache, nasal discomfort, oropharyngeal pain and sneezing). After these unsatisfactory results no further studies have been conducted.

What evidence for what mechanism of action?

In 1979, based on new findings about cerebral blood flow changes in migraine and CH [109], Sakai et al. first studied the cerebral vasodilator effect of 5% CO₂ inhalation for acute treatment and prevention in CH [110]. After inhalation during an attack, results showed impaired CO₂

responsiveness on the side of the headache but less on the non-headache side compared to healthy volunteers. Response returned to normal within 12 to 24h after end of headache. CO₂ inhalation seemed to be more effective in migraine than CH. The authors also observed more vasoconstrictive response and pain relief with 100% oxygen, and argued that oxygen might induce these effects by potentiated catecholamine and serotonin constriction, in CH but not in migraine, whereas 5% CO₂ might act by another mechanism. Comparable findings were also reported in a similar study [111]. Further studies described interactions between oxygen, CO₂ and CH attacks [112–114]. Paradoxically, these studies showed that hypoxemia induced CH attacks, leading to a higher level in end-tidal CO₂ in CH patients. Again, CO₂ inhalation seemed to induce CH attacks rather than treat them [115, 116]. However, intranasal CO₂ may act by a different mechanism than that reported for CO₂ inhalation. *In vitro* studies showed that CO₂ reduced intracellular pH, suppressing secretion of neuropeptides such as CGRP [117]. Thus, intranasal CO₂ might spread to the trigeminal nerve to reduce CGRP release, and other inflammatory mediators may be implicated.

What limitations and prospects?

Based on *in vitro* results, clinical trials using nasal CO₂ failed to demonstrate promising results for CH treatment. The pharmaceutical form used in the clinical trial may not have delivered a sufficient dose of CO₂ to the trigeminal nerve to inhibit CGRP release. At this point in time, at all events, nasal CO₂ seems not be a useful way to treat CH.

c. Emerging drugs in cCH

1) Ketamine

What clinical trials?

One study using ketamine is presently recruiting [118]. This phase I and II study's main objective is to investigate the effect of intranasal ketamine spray in 20 cCH patients. It is a single group assignment open-label study designed for proof of concept. cCH patients receive 15 mg ketamine in an intranasal spray of 100 µL aqueous solution. Administration is in one nostril under supervision of a nurse. Treatment is initiated at T0 under CH attack when headache pain exceeds 6

on pain NRS. The first intranasal dose of 15 mg is given at T0 and then 6-min intervals. At 15 minutes, after 3 doses (45 mg), it is determined whether the patient is sufficiently relieved (NRS < 4) or wants to receive rescue medication instead, or if pain is not sufficiently relieved and the patient wants to continue up to 5 doses (75 mg). Final assessment is performed at 30 minutes. Participants are followed up after 1-2 weeks by phone. The primary endpoint is $\geq 50\%$ reduction in pain on the 10-point NRS at 15 minutes. No results have yet been published.

What evidence for mechanism of action?

Ketamine is classified as a non-competitive NMDA receptor antagonist, but also has other various receptors and cellular processes [119]. It showed efficacy and safety in treatment of chronic pain [120]. Ketamine in CH was first studied by Granata et al. in 2016. Twenty-nine patients with CH (13 cCH and 16 eCH) who had been refractory to conventional treatment were treated with low-dose intravenous ketamine (0.5 mg/kg for 40-60 minutes) every 2 weeks apart from any CH attacks [121]. One to 4 administrations were performed, depending on treatment efficacy. Results showed that attacks were completely aborted for 3-18 months in 100% (n=13/13) of eCH patients and 54% (n=7/13) of cCH patients, and a majority of patients tolerated the treatment well. Subsequently, Moisset et al. reported 2 cases of intractable cCH treatment by ketamine infusion (0.5mg/kg over 2 hours) and showed complete relief in attack frequency and intensity for 1 patient and partial relief for the other for 6 weeks [122]. The mechanism of action may involve multiple pathways for both acute and prolonged effects. The immediate effect may be induced by activation of release of monoamines (serotonin, noradrenaline and dopamine) and inhibition of reuptake [123, 124]. It also may be attributable to NMDA receptor antagonism. Studies showed reduced levels of kynurenic acid (an endogenous NMDA receptor antagonist) in CH patients [18] and its ability to inhibit headache [125], suggesting overactivation of NMDA receptors in CH. This effect may involve reduction in NMDA-mediated “wind-up” in chronic pain [126].

What limitations and prospects?

Preliminary studies showed promising results, but with many limitations, such as the absence of placebo-control, maintenance of other therapies, or missing data for 3 eCH patients in Granata et al.’s study. This is why robust clinical trials are eagerly awaited, particularly with intranasal

ketamine administration. Limitations involve possible severe adverse events or misappropriation for recreational abuse [127]. However, ketamine could be a very interesting second-line treatment for refractory CH. This is all the more interesting as ketamine also showed promising results for the treatment of depression [128], frequently observed in CH patients [129]. Finally, if ongoing results prove non-significant, many other hypotheses could be further studied: magnesium combination [122], racemic pharmacological impact [130] or other NMDA drugs such as memantine [131].

2) *Botulinum Toxin A*

What clinical trials?

Two clinical trials are registered using botulinum toxin A (BTA), one completed [132] and one recruiting [133]. The first is a phase I and II study to investigate the safety issues of BTA injection to block the otic ganglion in cCH. Patients have cCH with ≥ 4 attacks per week. The study is randomized, parallel assignment, open-label. The main endpoint is number of adverse events recorded in a headache diary and open questions at office follow-up consultations. Participants are randomized in 2 arms: one receiving a 25 IU BTA injection toward the otic ganglion (ipsilateral to the pain) using image-guided navigation and the MultiGuide device, and one receiving the same injection at 12.5 IU. Patients are then followed up for 6 months and the promoter enrolled 10 participants. The study is now completed and results showed that BTA seems to be safe but unfortunately did not showed significant reduction in CH attacks frequency [132].

The second is a phase 3 study to investigate whether precise single injection of BTA reduces the frequency of attacks of refractory cCH. Patients have refractory cCH with dominant laterality ($> 80\%$) and with ≥ 8 attacks per week. It is a multicenter randomized placebo-controlled parallel-assignment quadruple-blind study. The main endpoint is change from baseline to week 5-8 post-intervention in mean number of CH attacks per week, on headache diary. Patients receive 1 injection of BTA (or placebo) 25 IU in 0.5 mL sodium chloride 0.9% in the headache side of the face, targeted at the sphenopalatine ganglion (SPG). The injection is assisted by a Multiguide navigation system to enable precise delivery. No results have yet been published. The promoter aims to enroll 112 participants and to complete the study in September 2025.

What evidence for what mechanism of action?

BTA is used to treat a variety of disorders characterized by pathologically increased muscle contraction [134]. The first case reports on BTA for CH were published in the late 1990s. In 1996, Ginies et al. first reported positive results in 3 out of 5 patients for BTA used to manage the end of a cluster period [135]. This was followed by other case reports: by Smuts and Barnard, who reported positive results in 2 out of 4 patients [136] and by Freund and Schwartz with 2 positive results in 2 patients [137]. Further open-label studies showed divergent results [138, 139], partially explained by failure to distinguish eCH versus cCH: BTA seems more effective in cCH than eCH [139]. In these studies, injection sites were not well specified and were only muscular, with a wide range of doses from 12.5 to 100 IU. There was renewed interest in BTA injections in the 2010s, as understanding of CH pathophysiology improved and new guided devices were developed and in the light of previous use of BTA in migraine. The implication of the trigeminal autonomic arc reflex through the SPG incited Bratbak et al. to perform an open-label study to assess BTA injection at 25 IU in SPG blockage to treat cCH patients [140]. The number of CH attacks was very significantly reduced in the intention-to-treat analysis (18 ± 12 per week at baseline versus 11 ± 14 per week after treatment; $p = 0.038$). Eleven adverse events were reported, including 1 severe (posterior epistaxis). Another observational long-term study of outcome in patients with intractable cCH treated with BTA injection toward the SPG reported similar results, with a reduced frequency of attack per month (57.3 ± 35.6 to 12.4 ± 15.2 at 18 months ($p = 0.018$) and to 24.6 ± 19.2 at 24 months ($p = 0.018$)) and of severe attacks per month (50.0 ± 38.3 to 10.1 ± 14.7 at 18 months ($p = 0.018$) and to 16.6 ± 13.7 at 24 months ($p = 0.028$)) [141]. In another study, Lampl et al. assessed the efficacy and tolerability of BTA injection in refractory cCH, with a different method [142]. The injections were innovative, following the Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy study protocol (PREEMPT) [143]: BTA was injected in different muscle areas of the head (frontalis, corrugator, procerus, temporalis, occipitalis, trapezius muscles and cervical paravertebral musculature) with doses from 5 to 40 IU in each area for a total 155 IU. Results showed a significant reduction in headache frequency (from 28.2 to 11.8 days at week 24; $p = 0.0001$) and in the intensity of remaining attacks, and an improvement in disability scores. 58.8% of participants reached at $\geq 50\%$ reduction in headache time (min) and 29.4% experienced 30-50% improvement. The promising results of this open-label study showed that another administration protocol could also be effective in cCH. In a recent systematic review,

Freund et al. analyzed data quality using PRISMA and GRADE guidelines [144] and concluded that evidence for BTA reducing CH attacks up to 50% was low quality, but that this was essentially due to sample size and lack of control group comparison.

To date, the action mechanism of BTA injections remains unclear, but many hypotheses are put forward. BTA might exert its action via multiple mechanisms in several steps [145]. First, there is a local effect of muscle relaxation directly after injection by inhibition of acetylcholine release [146]. Locally, BTA also inhibits release of CGRP and reduces CGRP-mediated sensitization [147]. Reduced sensitivity in ganglia might be mediated by a decrease in TRPV1 expression [145]. Then, due to its ability to undergo retrograde axonal transport, BTA might also modulated CGRP expression in dural trigeminal afferences [148]. Centrally, BTA also effects TRPV-1 expression in central systems [145]. Finally, BTA might have an indirect action on endogenous opioids [149] and GABA [150] by enhancing their neurotransmission in the trigeminal innervation region [151]. Thus, the mechanism of action of BTA still warrants further investigation, but all these effects may be at work at different levels.

What limitations and prospects?

The main limitation of BTA is the manufacturing process to develop a medication. BTA is the toxin produced by *C. botulinum*. Due to this provenance, BTA is processed in 3 stages (fermentation, purification and formulation), impacting cost [146]. Moreover, neutralizing antibodies can emerge after several injections, impairing efficacy [152]. Observational studies showed promising results for BTA, whether injected in the SPG or on the PREEMPT protocol. However, all these studies were observational and open-label, and a strong randomized placebo-controlled trial is still needed to assess efficacy BTA injection and introduce it in the American Headache Society guidelines [20]. Spotlights are now turned on the ongoing clinical trials.

d. Emerging molecules used in both eCH and cCH

1) *Zolmitriptan*

What clinical trials?

Two studies are currently registered using zolmitriptan. Zolmitriptan is not a brand-new therapeutic target or field in the therapeutic arsenal of CH, but innovative administration forms are being developed in these studies. The first is a phase II and III study to investigate the efficacy and safety of C213 for acute treatment of CH [153]. The study is active but not recruiting. Patients present either eCH or cCH with ≥ 1 year's progression and onset at < 50 years of age. It is a multicenter randomized (1:1:1) parallel-assignment quadruple-blinded placebo-controlled study. Patients self-administer zolmitriptan or placebo via a C213 microneedle system consisting of a proprietary disposable patch and a reusable applicator. The zolmitriptan-coated titanium microneedle array (3 cm² array) is attached to a 5 cm² adhesive patch. Patients are divided between 3 arms: 1) 1.9 mg zolmitriptan via one 1.9 mg patch and one placebo patch; 2) 3.8 mg via two 1.9 mg patches; and 3) placebo only. After randomization (day 1), patients have up to 48 weeks to treat cluster attacks with this system. Primary endpoints are the proportion of patients who achieve relief pain at 15 minutes and proportion who achieve sustained pain relief between 15 and 60 minutes, as measured by responding to questions in the electronic diary up to 1-hour post-treatment. Pain relief is defined as decrease in pain from severe to mild or none without the use of acute rescue, and pain sustained relief as a pain rating of mild or none at each time point without the use of medication. No results have yet been published. The promoter aims to enroll 120 patients and to complete study in April 2021.

The second study using zolmitriptan is a phase IV study to assess the efficacy and safety profile of zolmitriptan by sublingual administration for acute treatment of CH [154]. The status of this study is not known. Patients present either eCH or cCH. It is a multicenter randomized cross-controlled assignment open-label study. Patient are divided between 2 arms: active comparator group with 2.5 mg oral zolmitriptan, and experimental group with 2.5 mg sublingual zolmitriptan. The primary endpoint is points-reduction in pain on VAS several minutes after sublingual zolmitriptan, measuring points from 7-10 to 0-3 at 5, 10 and 15 minutes after administration. No results have yet been published. The promoter aimed to enroll 71 participants and study was to be completed in April 2019.

What's new and why zolmitriptan?

As it belongs to the same pharmacological class, the action mechanism of zolmitriptan is the same as for sumatriptan except that zolmitriptan is lipophilic and thus may have a more central effect

[155]. According to a large meta-analysis, sumatriptan seems to be more effective than zolmitriptan versus placebo (75% with sumatriptan and 62% with zolmitriptan) [156]. In some countries, zolmitriptan is already available as intranasal spray or orally [20]. However, there are disparities between European countries regarding health insurance cover and accessibility [157]. One may then wonder why a new clinical study using zolmitriptan is necessary. In this study, the innovation provided by zolmitriptan lies in the transcutaneous administration route. Sumatriptan had previously been developed under this form. In January 2013, the FDA approved Zecuity® (Teva Pharmaceuticals Industry Ltd, Tel Aviv, Israel), a transdermal system containing sumatriptan to treat migraine attacks [158]. However, it was recalled in June 2016 due to possible side-effects: serious burns and skin irritation [159]. Analysis of the development and approval process revealed a number of problems [160]: the rationale for development of a patch was weak; the FDA knew before approval about the possible side-effects; adverse-event reporting in the clinical studies was suboptimal; and endpoints had been changed during the trial. Social media and marketing may have contributed to the approval. Since then, sumatriptan patches have been discarded and manufacturers turned to zolmitriptan to develop a drug with transcutaneous administration.

What limitations and prospects?

Due to poorer efficacy than sumatriptan or oxygen for acute treatment and to marketing choice and shortage issues [157], zolmitriptan has been retrograded behind sumatriptan for headache treatment. However, a new administration route could restore its former position. Moreover, prescribers should be aware of potential cutaneous adverse events observed with sumatriptan.

2) *LSD: lysergic acid diethylamide*

What clinical trials?

One clinical trial using LSD is presently recruiting [161]. This phase 2 study's main objective is to investigate the effects of an oral LSD pulse regimen compared to placebo in patients suffering from CH. Participants are aged from 25 to 75 years, with eCH or cCH with predictable periods lasting approximately 2 months and attacks responding to oxygen. It is a double-blind randomized placebo-controlled two-phase cross-over study. LSD or placebo (LSD lookalike) is prescribed at the 100 µg per os 3 times within 3 weeks. The main endpoints are change in frequency and

intensity of CH attacks on a standardized headache diary. The promoter aims to enroll 30 participants and to complete the study in 2023.

What evidence for what mechanism of action?

LSD was first synthesized in 1938 by Albert Hofmann and its psychoactive effects were discovered in 1943. Sewell et al. were the first to suggest using LSD in CH treatment in a scientific article [162]. Based on testimony from a patient who experienced complete remission of his cluster periods when using LSD on a recreational basis, they launched an observational study on the subject. They administered a standardized questionnaire to CH patients who reported LSD use and analyzed responses from 53 patients. Results showed that LSD had been effective for acute treatment in 50% of patients and for prophylactic used in 88%. However, the authors highlighted several study limitations such as recall bias (retrospective report by the patient), selection bias and the fact that participants were not blind to treatment. Since then, most studies on the subject only reported use of illicit drugs in the general population, by questionnaire [163–165] or online forums [166, 167]. Interestingly, illicit drug users reported infrequent use of LSD, suggesting that non-daily posology might be effective. Many pharmacodynamic effects have been described for LSD [168], the most relevant to CH being interaction with serotonin receptors. Studies showed an ability to bind 5-HT receptors subtypes at different levels of affinity: 5-HT_{1A}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{5A}, 5-HT₆ and 5-HT₇ [169–172]. LSD is now considered as a mixed partial agonist of 5-HT₂/5-HT₁ receptors, explaining the duality between hallucinogenic and non-hallucinogenic effects respectively [168]. Due to the subhallucinogenic doses taken for CH treatment, benefits may involve a mechanism unrelated to the psychoactive effect on 5-HT₂ receptors [162]. LSD may act, like sumatriptan, as a 5-HT₁ agonist. Another interesting hypothesis concerns the dopaminergic action of LSD. In observational studies of LSD, CH patients used more than the general population. Govare and Leroux mentioned 3 hypotheses to explain this difference, including a common mechanism implicating dopamine, predisposing for CH attacks and drug abuse [6]. It is well known that dopaminergic pathways are implicated in addictive behaviors [173]. Case reports also showed that dopamine agonists can trigger [174, 175] or improve [176] CH attacks, and levels in such patients seem to be higher [177]. The pharmacodynamic effect of LSD also involves the dopaminergic system. LSD acts as both agonist and antagonist toward D₁

and D₂ receptors [178, 179]. Limitations and prospects are discussed in the following section on psilocybin, in an overview of illicit drugs.

3) *Psilocybin*

What clinical trials?

Two studies are registered and actively recruiting. The first is a phase I study to investigate the effects of an oral psilocybin pulse regimen in CH [180]. It is a randomized crossover-assignment triple-blind study. Participants have either cCH or eCH, treated by triptan no more than twice a week. Many primary endpoints are assessed by a headache diary maintain prior to, during and after the pulse regimen, to document frequency and intensity of headache attacks. Subjects are randomized to oral capsule placebo, low-dose psilocybin (0.0143 mg/kg), or high-dose psilocybin (0.143 mg/kg), in 3 experimental sessions at 5days' interval. At least 6 months after the last session, subjects may be invited for a second round, in which they are randomized to either low- or high-dose psilocybin. No results have yet been published. The promoter aims to enroll 24 participants and to complete study in June 2021.

The second is a phase I and II study to investigate the prophylactic effects of psilocybin in cCH only [181]. It is a single group assignment, open-label neuroimaging study. Patients receive a low-dose psilocybin (0.014 mg/kg) for 3 sessions at 1 week's interval. The primary clinical endpoint is change in headache frequency in number of attacks per week measured by a headache diary prior to, during and after sessions. Blood samples are also taken for plasma assay of psilocybin's main metabolite, psilocin. Patients are followed up for 4 weeks after the last dose of psilocybin. Patients also undergo fMRI before the first and after the last psilocybin session. The primary imaging endpoint is resting state functional connectivity (FC) fMRI analyses, including hypothalamic FC, comparing baseline to rescan, comparison with healthy controls, and correlation between headache frequency change and FC change. The promoter aims to enroll 20 participants and to complete the study in November 2020.

What evidence for what mechanism of action?

Psilocybin is a naturally occurring psychedelic prodrug produced by more than 200 species of mushroom. Use of psilocybin in CH has been described for centuries by traditional healers using *Psilocybe* mushrooms [182]. Matharu et al. first mentioned use of psilocybin to treat CH attacks in a scientific case report [183] of a patient taking 1 g of “magic mushrooms” (containing psilocybin), which rendered him pain free for 1 month. As previously described for LSD, Sewell et al. performed an observational study on psilocybin in CH [162]. Results showed that psilocybin was effective for acute treatment in 85% of patients (n=22/26) and for prophylactic used in 52% (n=25/45). Again in parallel to LSD, the main studies on the subject were observational, to assess the use of illicit drugs in CH populations [163–167]. Like LSD, psilocybin exercises its psychoactive effects by 5-HT_{2A} agonism and the therapeutic effect seems to be mediated by a different mechanism [184]. In contrast to LSD, psilocybin has no affinity for dopamine receptors and so certainly does not exercise its action via this mechanism [185]. Thus, the main hypothesis for its effects on headache is its interaction with the serotonin system, by disrupting the circadian rhythm through 5-HT_{1A}, 5-HT_{2C} or 5-HT₇, or through 5-HT_{2A} mediated gene induction [186]. In an fMRI study, a decrease with psilocybin intake was observed in cerebral blood flow in the hypothalamus, which is rather increased in CH attacks [187]. Thus, inhibition of the hypothalamus via direct electrical stimulation of serotonergic receptor expression could also be the action mechanism. However, this study was the only one which showed this effect, and all brain regions of interest were found to have decreased blood flow in the study [188]. The mechanism of action thus remains unknown and need to be further studied on imaging, as in the ongoing study described above.

What limitations and prospects for the use of illicit drugs?

Evidence-based medicine on patient practices with illicit drugs showed interesting results which need to be further explored in powerful clinical studies. Unfortunately, only a few studies are ongoing, doubtless due to the illicit status of LSD, and issues of addiction and hallucinogenicity, leading to many ethical discussions in the medical field [189–192]. One solution might be to use a new LSD derivate: 2-bromo-lysergic acid diethylamide (BOL-148). BOL-148 seems to be effective in preventing CH [184]. Compared to the illicit drugs, BOL-148 is non-toxic, non-hallucinogenic and not illegal. Again, results are only preliminary and need to be further studied.

4) *SOM230 - pasireotide*

What clinical trials?

One trial of SOM230 recently terminated [193]. This phase 2 study's main objective was to investigate the safety and effectiveness of SOM230 for CH treatment and to determine if further studies are warranted. Patients had eCH or cCH with an average 2-6 attacks per day, lasting at least 45 minutes without treatment; they were required to be able to self-inject medication subcutaneously. It was a multicenter non-randomized sequential assignment double-blind placebo-controlled single dose study. This study was planned to have 2 cohorts using a 1-sequence 2-period design to compare SOM230 vs. placebo. In cohort 1, SOM230 was administered in 1.5 mg doses and in cohort 2 in 0.9 mg doses. Two consecutive CH attacks were treated: the first attack with placebo (Period 1) and the next with SOM230 (Period 2). The primary endpoint was the number of participants with very severe, severe or moderate headache before administration that became mild or absent at 30 minutes. The study completed data collection in January 2020 and was terminated due to futility analyses in 28 participants. The primary endpoint was not achieved in the first sequential analysis, showing no significant difference between SOM230 1.5 mg and placebo (p-value = 0.698). The secondary endpoint (pain relief at 30 minutes) did also showed no significant difference (p-value = 0.385). No adverse effects were observed. Due to these results, cohort 2 was not launched and the study was terminated.

What evidence for what mechanism of action?

Endogenous somatostatin is widely distributed and is an important regulator of many endocrine and exocrine secretion organs [194]. In the 1980s, pain relief after somatostatin administration for CH was first reported by Scicuteri et al. [195]: intravenous somatostatin 25 µg/min for 20 min reduced pain intensity and duration in 72 attacks compared to placebo, to a degree comparable to ergotamine. A second study confirmed these findings on pain intensity with subcutaneous somatostatin compared to ergotamine [196]. Due to its short half-life (< 2min), effects on pain duration were less, and somatostatin was not suitable for use in acute CH treatment. Analogs of somatostatin with longer half-life, such as pasireotide (SOM230), could be an interesting response to this issue. Pasireotide is a cyclohexapeptide analog of the hormone somatostatin, with longer

half-life ($t_{1/2} = 12.5\text{h}$), developed for other diseases [194]. Before the study described above, there were no studies or case reports of pasireotide in CH. The mechanism of action of somatostatin and its analogs in CH may involve two different processes: somatostatin receptors are expressed in regions involved in pain processing and the hypothalamus [197]; and somatostatin also inhibited release of CGRP and substance P, neuropeptides implicated in pain and in CH [198].

What limitations and prospects?

Unfortunately, the only study using pasireotide failed to show promising results, stopping its use in CH. However, another somatostatin analog, octreotide ($t_{1/2} = 1.5\text{h}$) was also evaluated in CH treatment. A placebo-controlled double-blind crossover study using octreotide 100 μg in 57 patients (eCH and cCH) showed headache response in 52% compared to 36% with placebo [199]. Octreotide was inferior to sumatriptan [21] but might be an interesting second-line treatment for non-responders to sumatriptan. No further studies using octreotide have been developed, but this might be necessary.

5) CGRP monoclonal antibodies

What clinical trials for fremanezumab (TEV-48125)?

Three clinical trials are registered and all recently terminated [200–202]. These were all phase 3 studies. For the first two, the main objective was to compare the efficacy and safety between 2 dose regimens of fremanezumab versus placebo in adults for prevention of eCH [200] and cCH [201] respectively. They were multicenter randomized double-blind double-dummy placebo-controlled parallel-group studies. Schedules were similar in each arm: 3 subcutaneous injections at week 0, and 1 single injection at weeks 4 and 8. Interestingly, the arms differed between the two studies. In the eCH study, the drug administered according to the weekly schedule was placebo only in arm 1, fremanezumab 675 mg/placebo/placebo in arm 2 and fremanezumab 900/225/225 mg in arm 3, while the cCH study administered placebo only, fremanezumab 675/225/225 mg and fremanezumab 900/225/225 mg, respectively. The primary endpoint in eCH study was mean change from baseline in the weekly average number of CH attacks. In the cCH study, the primary endpoint was mean change from baseline in the overall monthly average number of CH attacks.

The eCH study was terminated as a result of a prescheduled futility analysis when 150 participants had completed the efficacy analysis. For the primary endpoint, the ANCOVA statistical test revealed no significant difference between placebo and fremanezumab groups (p-value = 0.9093 between placebo and fremanezumab 675 mg/placebo/placebo; p-value = 0.1345 between placebo and fremanezumab 900/225/225 mg). The cCH study was terminated as futility analysis revealed that the primary endpoint was unlikely to be met. Two-hundred fifty-nine patients were enrolled and ANCOVA showed no significant results between placebo and fremanezumab groups (p-value = 0.2741 between placebo and fremanezumab 675/225/225 mg; p-value = 0.3047 between placebo and fremanezumab 900/225/225mg).

The third study was a 68-week assessment of the long-term safety and efficacy of fremanezumab in cCH and eCH. It was a multicenter double-blind double-dummy study. Three arms were compared: subcutaneous fremanezumab at 225mg monthly, fremanezumab at 675mg quarterly and fremanezumab at 675mg loading dose followed by monthly fremanezumab at 225mg. Three primary endpoints were measured: adverse events, injection site reaction, and concomitant medication during the study period. The entire study was terminated after both eCH and cCH studies were terminated on prescheduled futility analyses.

What clinical trials for galcanezumab (LY2951742)?

Three clinical trials are registered: one active, not recruiting [203], and two completed [204, 205]. They are all phase 3 studies. In the two completed studies, the main objective was to evaluate the efficacy and safety of galcanezumab in participants with eCH and cCH respectively. They were randomized double-blind placebo-controlled studies. For cCH, a long-term open-label extension was also designed. Galcanezumab 300mg (or placebo) was administered subcutaneously every 30 days for 8 weeks in the eCH study and for 12 weeks in the cCH study. The primary endpoint was overall mean change from baseline in weekly CH attack frequency from week 1 through 3 for eCH and week 1 through 12 for cCH. The outcome was recorded in the patient's ePRO diary. The studies enrolled 109 and 240 participants for the eCH and cCH studies respectively according to the Clinical Trials registry. The results for eCH have already been published [204]; analysis focused on 106 patients, as 3 participants in the galcanezumab group did not have at least 1 injection. Results showed significant differences in mean reduction in weekly frequency of CH attacks across weeks 1 to 3 in the galcanezumab group (mean difference, 3.5 attacks per week;

95%CI [0.2-6.7]; p-value = 0.04). Seventy-one percent of patients in the galcanezumab group achieved at least 50% reduction in headache frequency at week 3 compared to 53% in the placebo group (p-value = 0.04). Mean change in weekly frequency of attacks converged after week 4. The only difference in adverse event rates was for injection-site pain in the galcanezumab group, with 8% of patients. Results of the cCH study have also been recently published [205]; analyses were made in 237 patients. Statistical tests did not show significant differences between groups for the primary endpoint (p-value = 0.334) or for one of the main secondary endpoints.

The third currently active study is primarily intended to assess the long-term safety and tolerability of galcanezumab in cCH and eCH patients who have completed the two previous studies. The two primary endpoints are adverse events and suicidal ideation/behavior. No results have yet been published, but the previous studies suggest that significant differences are unlikely.

What evidence for what mechanism of action?

Calcitonin gene-related peptide (CGRP) is a 37-amino-acid neuropeptide discovered in 1982 [206]. It is released into the blood from activated trigeminal sensory afferents and the trigeminal nucleus caudalis in response to stimulation [207]. Binding a high-affinity CGRP receptor or calcitonin receptor-like receptor/receptor activity-modifying protein 1 complex, CGRP induces cranial vessel vasodilatation and centrally modulated vascular nociception [208, 209]. CGRP can also bind amylin receptor 1 (AMY₁) with high affinity, but its involvement in CH has not yet been explored [210]. Fremanezumab and galcanezumab are monoclonal antibodies (MAB) targeting the CGRP ligand, preventing fixation on the receptor and thus its headache effects [211–213]. Due to this competition and considerable evidence for CGRP involvement in migraine attacks, these molecules were first developed to treat migraine. Phase II and III studies demonstrated efficacy and safety [217], and they are now indicated by the EMA for migraine prophylaxis in adults who have at least 4 migraine days per month. Observations of increased CGRP plasma levels in CH suggested applying CGRP-MAB in CH prevention. The increase was sensitive to sumatriptan and oxygen therapy, with rapid decrease in CGRP levels [218, 219]. Thus, anti-CGRP MABs were explored for CH treatment. Unfortunately, the above phase III studies showed mixed results. In June 2019, galcanezumab was the first anti-CGRP MAB approved for eCH treatment by the FDA [220]. Paradoxically, in February 2020, the EMA refused a change to the marketing authorization for the galcanezumab specialty Emgality® [221], stating that “*Results from the single study in patients with episodic cluster headache did not show clearly that Emgality® is effective for*

preventing attacks.” In parallel, fremanezumab’s manufacturer discontinued its clinical development program for CH due to the unsatisfactory results of a phase III study.

What limitations and prospects?

Galcanezumab is still in the pipeline for FDA approval in eCH. Further studies might be needed for EMA approval. Correctly performed phase III studies, avoiding bias and limitations, excluded fremanezumab for CH treatment. Two pathophysiological hypotheses may explain the mixed results. Firstly, Goadsby reported that not all patients released CGRP at the same level, and also with possible individual variation over time [27]. Secondly, it is well known that antibodies have difficulty in crossing the blood-brain barrier, limiting them to peripheral effects, whereas CH may involve a central mechanism, thus decreasing impact. Although fremanezumab and galcanezumab did not show significant results, two other anti-CGRP MABs, eptinezumab (ALD403) and erenumab (AMG334), may prove more effective. These molecules are already approved for migraine treatment by the FDA (eptinezumab) and by the FDA and EMA (erenumab). This all the more interesting as erenumab has a mechanism of action that is slightly different than other MABs, targeting CGRP receptors [222]. Moreover, erenumab already showed promising results in CH, but further studies are warranted [223]. Finally, another pipeline in CGPR targeting is the small CGRP receptor antagonist called gepant. First-generation gepants were not satisfying due to severe hepatotoxicity, but the new generation showed efficacy and safety in recent clinical trials in migraine [224]. Once again, if these molecules show promising results, further studies in CH might be designed. Despite the inconsistent results with anti-CGRP MABs, drug candidates targeting this neuropeptide pathway remain relevant.

6) *Sodium oxybate*

What clinical trials?

One clinical trial, started in December 2015, using sodium oxybate (SO) is registered [225]. The current status of the trial is not known, but the promoter confirmed study completion in June 2017, although no results have been published. This phase 3 study’s main objective was to assess the safety and efficacy of SO in the prophylaxis of headache and sleep disorders. Patients were 18 to 75 years old, with eCH or cCH, and with nocturnal pain attacks disturbing sleep quality. It was a

placebo-controlled double-blind randomized parallel group study. SO was administered orally, at 3 to 9g per night, starting with 3g in 2 nightly doses of 1.5g (1 at bedtime and the other 4 hours later). Dosage was gradually increased by steps of 1.5 g every second night until treatment response and maintained for a 14 day period. The effect of SO was assessed via pain and sleep diaries for the 14 days of stable treatment. The main endpoint was frequency of nocturnal pain attacks. The promoter aimed to enroll 60 participants but no updated data have been published.

What evidence for what mechanism of action?

We noted above that CH follows a circadian rhythm. Approximately 80% of patients report that both eCH and cCH attacks strike during sleep [226]. The EMA authorizes SO to treat narcolepsy with cataplexy, well-known to be a sleep disorder. It also was shown to reduce pain in fibromyalgia syndrome. Based on these postulates, Khatami et al. reported use of SO in CH [227]; long-term efficacy for headache and sleep disorder was assessed in patients with cCH. Four patients received oral SO on the same schedule as in the clinical trial above. This study provided class IV evidence that oral SO at night improves sleep and reduces the intensity and frequency of headache. Effects were long-lasting, for a mean 19 months, in 3 cases and transient, for 8 months, in 1. Despite the absence of a placebo control group, there was much evidence of a real effect of SO: dose-dependent response, resurgence of CH attacks after treatment discontinuation, and improvement in sleep quality confirmed by both slow-wave sleep recording and patients' diaries. Unfortunately, the study suffered from limitations in its design (no placebo control, single center), persistence of daily headaches and long-term monitoring of adverse events. Hidalgo et al. also reported the case of a 61 year-old man suffering from eCH, treated successfully with SO [228]. Again, posology was increased gradually on the same schedule, and improved CH frequency and intensity and sleep quality. SO is the sodium salt of an endogenous hormone synthesized in brain gamma-hydroxybutyric acid (GHB), which is also its main metabolite. Due to its structural similarity to gamma-aminobutyric acid (GABA), it binds GABA receptors. Benzodiazepines, known to bind GABA_A receptors, are less effective in CH treatment. Thus, SO and GHB might exercise their effects by one of their many other mechanisms, such as GABA_B receptors, serotonin turnover or dopamine release [229].

What limitations and prospects?

The use of SO and GHB as medical drugs is also questioned because of the risk to misuse for illegal purposes [230]. High-dose SO and GHB abuse can lead to severe central nervous system adverse events, sometimes causing withdrawal symptoms [231]. However, a specialty named Xyrem® is already authorized by the EMA and FDA for the treatment of narcolepsy with cataplexy. The phase IV post-marketing study demonstrated safety on a program of controlled prescription and dispensation [232]. Thus, use of SO in CH could be modeled on this use in narcolepsy, avoiding the risk of illicit use. Meanwhile, further studies are needed in this indication to assess efficacy.

LIMITS OF RESEARCH IN THE CH FIELD

As mentioned, the majority of recent clinical trials focused on new pharmacological treatments (n= 22/38). However, it is important to bear in mind that surgery is also part of the therapeutic arsenal. Neurostimulation at different levels, such as the hypothalamic region, the GON or the SPG, is the most recent and effective technique [19, 20]. Only hypothalamic and SPG stimulation have been studied in class I clinical trials [233, 234]. SPG stimulation showed superior efficacy versus sham stimulation, while hypothalamic stimulation did not. The SPG is thus a promising target in surgery, and 4 clinical trials focused on it. The first has been completed, and showed that low-frequency stimulation of the SPG induced autonomic symptoms but was not sufficient to induce a cluster-like attack [235]. The second study assessed the safety and performance of the Pulsante Microstimulator System implanted in the SPG for 5 years [236]. The third study still ongoing, and aims to investigate the effectiveness and safety of SPG pulsed radiofrequency stimulation versus traditional SPG nerve block [237]. The fourth study, recently posted in April 2020, aims to evaluate the safety and efficacy of intra-arterial delivery of dexamethasone and ketorolac into the arteries supplying the SPG in patients with refractory migraine, CH and trigeminal neuralgia [238]. Other non-pharmacological therapy trials are also ongoing: physiotherapy [239], Atkins ketogenic diet [240] or continuous positive airway pressure [241]. Concerning the Atkins ketogenic diet, results have been posted and suggest that ketogenesis could be helpful for eCH and cCH patients. This diet modulate cortical excitability or dampen neuro-inflammation [242]. Although pharmacological therapies are predominant, non-pharmacological therapies also merit attention.

As previously outlined, the emergence of new treatments in CH is presently deadlocked. The main limitation for the discovery of new therapeutics is that pathophysiological mechanisms are not yet well understood. This is why other clinical trials are also ongoing, for better understanding of these mechanisms. A systematic search of the clinicaltrials.gov website for the last 5 years retrieved 9 clinical trials trying to elucidate or identify new pathways and hypotheses for future treatments. In this field, we can distinguish trials involving new biomarkers such as CGRP or more recently PACAP-38 [243–245], those investigating circadian rhythm [246–248], and those investigating prognostic factors [249, 250]. More recently, one study was launched to assess the involvement of the autonomic nervous system [251]. Although studies exploring pathophysiology are ongoing, they are too few in comparison to therapeutic research. As shown in part 3 above, the development of new drugs requires understanding pathophysiological mechanisms, developing new devices and discovering new targets. For example, identifying new neuropeptides involved in CH such as CGRP allowed researchers to target these peptides and develop new therapies. Unfortunately, anti-CGRP showed mixed results. The research into BTA also illustrates this necessity. Studies showing the involvement of the SPG in CH and the development of new multiguided devices to target the injection site more accurately have opened new therapeutic fields. While research is mainly focused on developing new therapies, fundamental studies are also still needed to elucidate the pathophysiology of CH in order to develop new concepts and targets.

This lack of research in CH can also be explained by the absence of reproducible animal models. On a review of the literature, no animal model stands out as a reference in CH. Many protocols have been described to develop cluster-like attacks, and are based on the same principle used to induce attacks through drugs such as capsaicin, nitroglycerin (NTG) or nitric oxide or a mixture of inflammatory mediators. Models using capsaicin differ in choice of administration route, whether applied in oral or nasal mucosa concentrate from 0.01 to 1 mM [252] or injected in the orofacial region with a wide range of doses from 0.25 to 500 μ g [253]. In these studies, capsaicin induced clinical pain responses such as increased grooming or lacrimation, and physiologic responses such as increased blood flow, activation of autonomic nerves and release of neuropeptides. These clinical and biological features are also observed in CH. The model also showed response to many therapies used in CH, suggesting that it could be useful for exploring CH. The main limitation of capsaicin is its short half-life, entailing short attack observation. The use of NTG in animal models

was also been described, with various modalities [254, 255]. NTG induced cluster-like attacks due to its ability to release CGRP, activate autonomic activity and vasodilate vessels and to direct central effects in animals [254, 256]. It was also reported in humans to activate brain areas involved in pain processes, such as the anterior cingulate and insular cortex, posterior thalamus or hypothalamus [13]. Protocols using mixtures of inflammatory mediators have also been used to explore CH [257]. This model is different, being administered directly into the dura mater. Finally, direct stimulation of the superior salivatory nucleus was also reported to cause similar cluster attacks by activating the trigeminocervical complex and inducing autonomic symptoms [258]; unfortunately, these protocols are difficult to implement and incur high risk for animal. All of these protocols suffer from the same limitations: the difficulty of correctly discriminating CH from other types of headache (especially migraine), and of assessing pain in animals [259]. This absence of animal models in pre-clinical studies leads to a lack of reproducibility for exploring CH pathophysiology, and research in animal models remains difficult.

The emergence of new drugs is also based on patient practices with illicit drugs. Although the placebo effect seems to be very low in CH patient [260], robust clinical studies are needed with placebo-controlled randomized double-blind designs. We have seen, with many examples, that open-label or retrospective studies with promising results collapsed when a powerful phase 3 study was performed. Pageler et al. learned from their own studies, and explained the main limitations to be avoided in clinical trials in CH research [261]. Likewise, the International Headache Society issued guidelines for clinical studies in CH; however, these date back to 1995 and might usefully be revised [262].

To sum up, treatments currently used in CH have several limitations and development of new drugs is required. Research is limited by lack knowledge of pathophysiology, lack of animal models. In the last 5 years, no brand-new treatment has emerged, but promising drug studies are ongoing. According to the literature and guidelines, researchers should be aware of many limitations in study protocols: concomitant medication, sufficient number of enrolled patients, patient compliance to protocol, study design, which can restrict patient recruitment, and differences patient profiles, especially between eCH and cCH.

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Figure 1. Flowchart of research for new clinical trials from 2015 to 2020. Search results on *clinicaltrials.gov* found 39 studies. Twenty-one studies were discarded from the analyses due to observational study design or non-innovative drug study. Eighteen studies were analyzed involving 11 different drugs. An extensive bibliographic search was performed due to lack of results with the systematic search on PubMed.

Table I. Summary of most relevant drugs used in CH treatment according to their therapeutic field and with their possible mechanism of action and limits.

Table II. Summary of new emerging therapies (n=11) in CH research from 2015 to 2020. Table resume their possible mechanism of action, number of clinical trials, phase study and status of clinical trials according to *clinicaltrials.gov*. Status of clinical trial is determined as follows: T=Terminated; R=Recruiting; ANR=Active Not Recruiting; U=Unknown; C=Completed; NRY=Not Recruiting Yet.

Indication	Drugs	Possible mechanisms	Limits
Acute Attacks	Sumatriptan	5-HT _{1B/1D/1F} agonism	Resistance Contraindications
	Oxygen	Inhibition of the parasympathetic activity Inhibition of neurogenic plasma protein extravasation Vasconstriction	Misuse Cost
Prevention	Verapamil	Vasoconstriction Inhibition of CGRP release Modulation of the circadian rhythm	Cardiotoxicity Binding follow-up Interactions Time to efficiency
	Lithium	Modulation of serotonin release Rapid eye movement sleep Modulation of opioid receptor	Narrow therapeutic window Long-term adverse events Interactions
	Topiramate	Augmentation of GABA _A activity Inhibition of voltage-gated Na/Ca channels Inhibition of glutamate-mediated neurotransmission	No consensus Absence of dose-effect correlation Adverse events
Transitional	Corticosteroids	Reduce CGRP release Increase melatonin release	No consensus Long-term adverse events Only transitional

Indication	Drugs	Possible mechanisms	Number of studies	Study phase	Status
Acute Attacks	Zolmitriptan		1	Phase 4	
	Ketamine	Activation of monoamines NMDA antagonism NMDA mediated "wind-up"	1	Phase 1-2	R
	Pasireotide SOM230	Reduce pain process and hypothalamus activity Inhibition of pain neuropeptides release	1	Phase 2	T
	Nasal carbon dioxide	Potentiate catecholamine and serotonin constrictive effect Reduce CGRP release	1	Phase 2	T
Prevention	C213 (Zolmitriptan)	5-HT _{1B/1D/1F} agonism	1	Phase 2-3	ANR
	Psilocybin	Interaction with serotonergic system Decrease hypothalamus activity	2	Phase 1-2 Phase 1	R R
	LSD	Interaction with serotonergic and dopaminergic system	1	Phase 2	R
	Fremanezumab TEV-48125	CGRP blockage	3	Phase 2 Phase 3 Phase 3	T T T
	Galcanezumab LY295142	CGRP blockage	3	Phase 3 Phase 3 Phase 3	ANR C C
	Sodium oxybate	GABA _B agonism Serotonin turnover Dopamine release	1	Phase 3	U
	Botulin toxin A	Inhibition of acetylcholine release Inhibition of CGRP release Decrease of TRPV1 expression Enhance opioid and GABA action	2	Phase 1-2 Phase 1	C C
	Civamide	TRPV1 modulation Decrease vasodilatation Decrease neurotransmitter release	1	Phase 3	NRY

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Research on *clinicaltrials.gov* with the disease term "Cluster Headache" from 2015 to 2020

fcpl12636_f1.pdf

n=39

Analysis of clinical trial involving new emergent therapies

n=11 drugs
(18 studies)

For each drug: systematic research on pubmed with the following equation:
("name of the molecule" [nm]) AND "Cluster Headache" [MeSH Terms]

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Extended bibliographic search to complete information on Table 2