PROPOSAL FOR THE ADDITION TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES OF SUBCUTANEOUS SUMATRIPTAN FOR THE ACUTE TREATMENT AND VERAPAMIL AND PREDNISOLONE FOR PREVENTION OF CLUSTER HEADACHE IN ADULTS

This is a joint application from two scientific societies (the European Headache Federation [https://www.ehf-headache.com] and the International Headache Society (https://ihs-headache.org/en/]) and two charities (Lifting The Burden [https://www.l-t-b.org] and DREAM [Disease Relief by Excellent and Advanced Means: https://www.dream-health.org/a-new-public-health-model/?lang=en]).

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Section 1: Summary statement of the proposal

This submission calls for the addition of sumatriptan (subcutaneous), verapamil and prednisolone to the WHO Model List of Essential Medicines (EML) for the treatment and prevention of cluster headache (CH) in adults.

CH is a highly debilitating neurological disorder characterized by excruciating, recurrent attacks of unilateral pain, typically localized around the eye or temple, and often accompanied by autonomic symptoms such as tearing, nasal congestion, and ptosis *(1)*. The attacks last 15 -180 minutes and occur in bouts. In its most typical form (episodic CH) bouts last weeks or months with frequency of attacks varying from once every other day to 8 times/day *(2)*. In the chronic form, attacks recur without free intervals longer than 3 months. During the attacks, pain is excruciating, explosive, and nonfluctuating, with an intensity of 10 on a 0-10-point scale for 2/3 of the subjects *(3, 4)*. These intense, recurring episodes significantly disrupt the lives of affected individuals, underscoring the urgent need for both acute and preventive treatment options to reduce the frequency and severity of attacks.

Sumatriptan (subcutaneous) is the preferred medication for the acute management of CH attacks, offering rapid symptom relief (within 10 minutes of administration) for many patients *(5)*. Its fast action is essential for managing the excruciating pain of CH attacks.

Verapamil is the first-line preventive treatment for CH in current clinical practice *(6)*. It is effective in reducing attack frequency and severity and is well-tolerated.

Prednisolone is recommended for short-term use as a bridging therapy during the initiation or adjustment of preventive treatments. Its potent anti-inflammatory properties provide rapid stabilization of CH, helping to reduce attack frequency and severity until long-term treatments, such as verapamil, take full effect *(7)*.

Section 2: Consultation with WHO technical departments

During the preparation of this application, multiple consultations were held with the relevant WHO technical departments to ensure alignment with global public health priorities and technical standards. Specifically, the Brain Health Unit of the WHO Department of Mental Health & Substance Use provided essential input throughout the drafting process.

Key individuals consulted include:

- **Dr. Tarun Dua**, Brain Health Unit, WHO Department of Mental Health & Substance Use
- **Dr. Nicoline Schiess**, Brain Health Unit, WHO
- **Rodrigo Cataldi**, Brain Health Unit, WHO

These experts provided guidance and feedback on the proposal, offering critical assessments of various drafts and ensuring that the application is comprehensive, scientifically robust, and relevant to global public health needs.

Section 3: Other organization(s) consulted and/or supporting the submission

In addition to the four joint applicants (IHS, EHF, LTB and DREAM), we have also consulted the European Migraine and Headache Association https://www.emhalliance.org/, who is in full support of this application.

Section 4: Key information summary for the proposed medicines

International nonproprietary name (INN)	Verapamil	Sumatriptan	Prednisolone
Anatomical therapeutic chemical (ATC) code	C08DA01	N02CC01	H02AB07
Indication(s): ICD11 codes	Preventive treatment Cluster Headache (ICD-11: 8A84.0)	Acute treatment Cluster Headache (ICD-11: 8A84.0)	Bridging treatment Cluster Headache (ICD-11: 8A84.0)
Dosage form(s) and strength(s)	- Immediate-release tablets: 40 mg, 80 mg, 120 mg - Extended-release tablets: 120 mg, 180 mg, 240 mg	Subcutaneous injection: 6 mg/0.5 mL pre-filled syringe or autoinjector	Oral tablets: 5 mg, 25 mg
On the EML	Yes, for other indications	No	Yes, for other indications

Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

This submission relates to the individual listings of subcutaneous sumatriptan, verapamil and prednisolone under a new heading of Cluster Headache in the WHO Model List of Essential Medicines (EML).

Sumatriptan (subcutaneous) is a selective 5-HT1B/1D receptor agonist that works by constricting intracranial blood vessels and inhibiting the release of pro-inflammatory neuropeptides, which reduces pain transmission during CH attacks. The rapid onset of action of sumatriptan, particularly when administered subcutaneously, allows for effective relief of acute cluster headache attacks, often within 10-15 minutes *(8, 9)*. This rapid relief is critical for managing the intense, debilitating pain associated with cluster headaches.

Verapamil has a well-established role as the first-line preventive treatment for CH, significantly reducing the frequency and severity of attacks. It is the only calcium channel blocker with substantial evidence supporting its efficacy in this specific indication. Other calcium channel blockers, such as diltiazem, have not demonstrated comparable efficacy, making verapamil the preferred option for preventing CH.

Prednisolone is frequently used as a short-term bridging therapy during the initiation or adjustment of preventive treatments, such as verapamil. It provides quick symptom relief while the longer-term therapies take effect, making it an essential part of the transitional management of CH. Other corticosteroids, such as dexamethasone and methylprednisolone, have not demonstrated the same level of efficacy or widespread use in this context, justifying the selection of prednisolone.

Each medicine plays a unique role in addressing the acute and preventive needs of patients, and no other alternatives within their respective pharmacological classes offer the same level of efficacy and safety in the treatment of this debilitating condition.

Section 6: Information supporting the public health relevance

CH, a severe primary headache disorder, is one of the most debilitating neurological conditions, affecting approximately 1 in 1,000 people globally, with a higher prevalence in males *(10)*. CH is characterized by periods, lasting weeks or months, of frequently recurring attacks of excruciating unilateral pain, typically around the eye or temple, usually accompanied by extreme agitation and autonomic symptoms such as tearing, nasal congestion, and ptosis *(11)*. These attacks, although short-lasting, are totally disabling. They may recur several times a day, very substantially impacting the productivity and quality of life of those affected not only during the attacks but throughout the cluster period. Attacks require very rapid intervention coupled with preventative management to alleviate their profound burden on individuals.

Although less common than migraine, CH imposes substantial lost-health and economic burdens, with high healthcare costs *(12)*. In low- and middle-income countries (LMICs), the lack of access to effective treatments exacerbates suffering, highlighting the need for affordable and accessible medications.

The currently available treatments for migraine, including propranolol and amitriptyline, are not effective for CH. Inclusion of sumatriptan (subcutaneous), verapamil and prednisolone in the EML, promoting access to the most effective therapies, would greatly enhance the global management of CH and address a gap in the treatment of the most painful of the primary headache disorders.

Section 7: Treatment details

Dosage and Administration

- **Sumatriptan** (subcutaneous):
  - **Standard Dosage**: 6 mg administered subcutaneously, with a maximum daily dose of 12 mg.
  - **Elderly Patients**: same dosage with added cardiovascular monitoring due to increased risks.
- **Verapamil:**
  - **Immediate-Release Tablets**: Start with 80 mg to 120 mg three times daily, with a gradual increase based on response and tolerance, up to 480 mg daily. In some cases, doses up to 720 mg daily may be necessary.
  - **Extended-Release Tablets**: Starting dose of 160 mg to 240 mg once daily, adjusted as needed, typically up to 360 mg to 480 mg daily.
  - **Elderly Patients**: Lower starting doses (e.g., 40 mg three times daily) with careful monitoring for side effects such as bradycardia.
- **Prednisolone:**
  - **Standard Dosage**: 40–60 mg per day, followed by a gradual taper over 2–3 weeks based on patient response.
  - **Elderly Patients**: Lower starting doses with close monitoring for corticosteroid-related side effects such as osteoporosis and adrenal suppression.

Monitoring and Diagnostic Requirements

- **Sumatriptan**: Cardiovascular risk assessment is essential, with ongoing clinical monitoring during use.
- **Verapamil**: Baseline and periodic ECG monitoring is required to detect potential cardiac issues such as bradycardia or heart block.
- **Prednisolone**: Monitoring for corticosteroid-related side effects, including hyperglycemia and hypertension, is essential during treatment.

Treatment Administration Requirements and Setting

- **Sumatriptan (subcutaneous)**: Can be self-administered after appropriate patient education.
- **Verapamil**: Typically administered in outpatient care with ECG monitoring available. Extended-release formulations may be preferred for patients who benefit from once-daily dosing.
- **Prednisolone**: Administered orally in primary care settings, with close follow-up to manage tapering and monitor for side effects.

Section 8: Review of evidence for benefits and harms

We conducted a systematic search of the studies evaluating the efficacy of verapamil, subcutaneous sumatriptan and prednisone/prednisolone in the PubMed, Web of Science and Cochrane databases until October 2024. The PRISMA flowcharts are given in Figure 1, 2 and 3. We included studies perfomed in adults and meta-analyses, excluding case reports, clinical notes, animal studies and studies that evaluated the efficacy of the other formulations of these drugs. Characteristics of the studies and meta-analyses supporting the efficacy of subcutaneous sumatriptan verapamil or prednisone/prednisolone in managing CH are given in Tables 1 and 2. We also performed the quantitative analysis of the available data reported in the studies. Proportional meta-analysis was used for overall estimations of complete response rate and 50-100% response rate and their confidence intervals *(13)*. Relative risk ratios were used to assess statistical differences of the pooled dichotomous data. According to the heterogeneity test and I^2 value, differences were tested using the common effect model or random effects model. We assessed the risk of bias using a modified Cochrane risk of bias tool (RoB2.0).

Verapamil

Verapamil, a first-line prophylactic treatment for CH, was consistently found to be highly effective in reducing attack frequency. The analysis included data from five studies (two of which were RCTs) that have investigated the prophylactic effect of verapamil in CH (Figure 1). The first open-label study included five patients with cCH who received verapamil 160–720 mg *(14)*. A subsequent open-label trial in 48 patients with cluster headache showed a reduction in headache frequency of more than three-quarters in 69% of patients *(15)*. Approximately 87% of patients reached either a complete response or a 50% or more reduction in headache frequency *(15-17)*. 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 *(17)*. 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 *(18)*. 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 *(19)*. Patients treated with verapamil reported a mean reduction of 1.3 CH attacks compared to only 0.28 in the control group *(19)*. Figure 2 shows verapamil responsiveness across studies that reported complete response or ≥50 % reduction in the attack frequency.

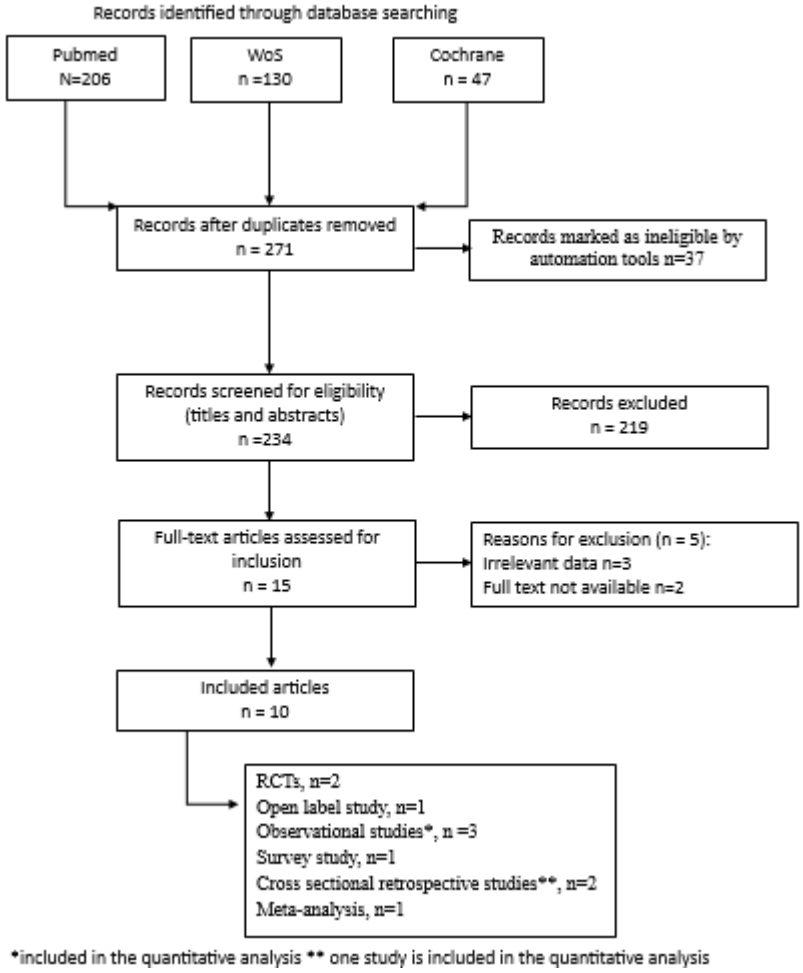
According to the European Academy of Neurology (EAN) guidelines, verapamil is effective in reducing the frequency and severity of cluster headache attacks, with dosages typically starting at 240 mg per day and titrated based on patient response and tolerance. In a double-blind, placebo-controlled trial, 80% of patients with episodic cluster headaches achieved a 50% reduction in attack frequency while on Verapamil *(12)*. However, the therapeutic effect may take 14–21 days to develop, making corticosteroids a temporary option when rapid action is needed, especially in short-lasting episodic cases. Typical dosing for verapamil begins at 80 mg three to four times daily, with gradual increases and ECG monitoring due to potential cardiac side effects, including bradycardia and conduction abnormalities. Regular follow-ups with ECG are essential, as approximately one-third of patients may develop bradycardia and one-fifth may experience ECG changes. Verapamil was the most frequently used preventive treatment for cluster headaches, with 55% of participants actively using it *(20)*. Of these, 57% achieved at least a 50% reduction in attack frequency or intensity, though only 14% of users reported complete relief. The effectiveness did not significantly differ between high-dose users (≥500 mg/day) and low-dose users, nor did it show a substantial correlation with age, sex, or headache duration.

Lee et al. found that verapamil was widely used as a preventive treatment for CH, with a prescription rate of 67.5%. Among patients compliant with the treatment, 90.8% experienced a significant reduction in attack frequency, highlighting verapamil's effectiveness. The median dosage was 180 mg per day, with an interquartile range of 180-240 mg. Verapamil's efficacy was particularly high when used in combination with systemic or suboccipital steroids, showing a response rate above 80% across treatment regimens *(21)*.

Verapamil emerged as the most frequently prescribed prophylactic treatment for CH, given to 60 of the 114 patients (87.25%) receiving preventive care. Of those treated with verapamil, 50.79% achieved a complete response, while 31.75% showed a partial response, underscoring its efficacy in managing symptoms *(22)*.

The results from studies on verapamil as a prophylactic treatment for CH indicate its frequent use and effectiveness, especially when compared to other preventative medications. In one study, verapamil was the first-line choice and demonstrated significant efficacy in reducing headache frequency and severity in many patients, although it has a delayed onset, typically showing full effect after 10-14 days *(23)*. In the patient cohort studied, verapamil was generally well-tolerated with moderate to high levels of effectiveness, particularly in episodic CH as compared to chronic cases. Some patients combined verapamil with other medications like prednisone or topiramate, which also provided enhanced effects in certain cases. However, the use of verapamil in combination treatments did lead to reports of adverse effects, particularly in female patients *(23)*.

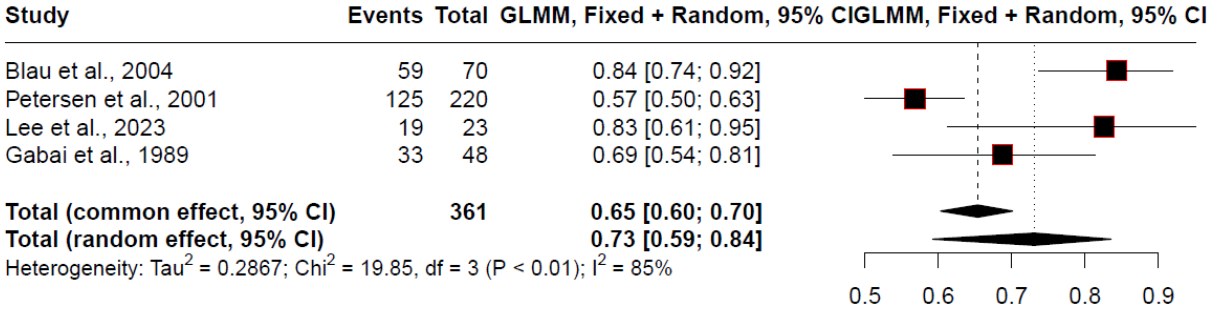
Figure 1 - Flowchart of the literature search of the studies supporting the efficacy of Verapamil



*included in the quantitative analysis ** one study is included in the quantitative analysis

The pooled analysis of the available data showed that 73% of the patients (95%CI:0.59-0.84)(I^2= 85%,p<0.01) who received verapamil reached either a complete response or a 50% or more reduction in the attack frequency (Figure 2).

Figure 2 - Forest plot showing verapamil responsiveness across studies that reported complete response or ≥50 % reduction in the attack frequency



Sumatriptan

Figure 3 shows the search output. A scoping review included multiple RCTs comparing triptans in CH with placebo *(24)*. This review showed that subcutaneous 6 mg Sumatriptan is highly effective in the acute management of cluster headaches, providing rapid relief within 10–15 minutes of administration according to the pooled analysis the data of two RCTs *(25, 26)*. These studies provided data from a total of 131 participants who were treated with subcutaneous sumatriptan. The proportion of patients who were pain-free at 15 minutes with sumatriptan 6 mg was 48% and 17% with placebo. The relative benefit of treatment compared with placebo was 2.8 (1.8 to 4.2), with a number needed to treat (NNT) of 3.3 (95% CI 2.4–5.0). The rates for headache relief after 15 min were 75% and 32%, resulting in a NNT of 2.4 (95% CI 1.9–3.2) *(24)*. A multicenter study conducted at 52 centers evaluated 6353 attacks from 138 patients treated with subcutaneous sumatriptan for a period of up to three months and showed headache relief in 96% of the treated attacks at 15min after the injection *(25)*. Another multicenter long-term study that evaluated a total of 2031 attacks in 52 patients reported response to subcutaneous sumatriptan in 88% of the attacks during a period of up to one year and more than 90% of the attacks resolved completely within 15 min in 42 % of the patients *(27)*. The effect after subcutaneous sumatriptan occurs much more quickly than that of the intranasal formulation, which is particularly important considering that attacks only last for up to 180 min. The network meta-analysis investigating effects of acute therapies for CH showed also that the response to sumatriptan was better than those to intranasal zolmitriptan or subcutaneous octreotide *(28)*. Quantitative analysis of pooled data comparing subcutaneous sumatriptan and placebo for pain freedom at 15 minutes and the risk of bias of the eligible trials are given in Figure 4. In this analysis, the relative benefit of subcutaneous sumatriptan 6 mg at 15 minutes compared to placebo was 2.77 (95%CI:1.82-4.21)(I^2= 22%, $p<0.01$).

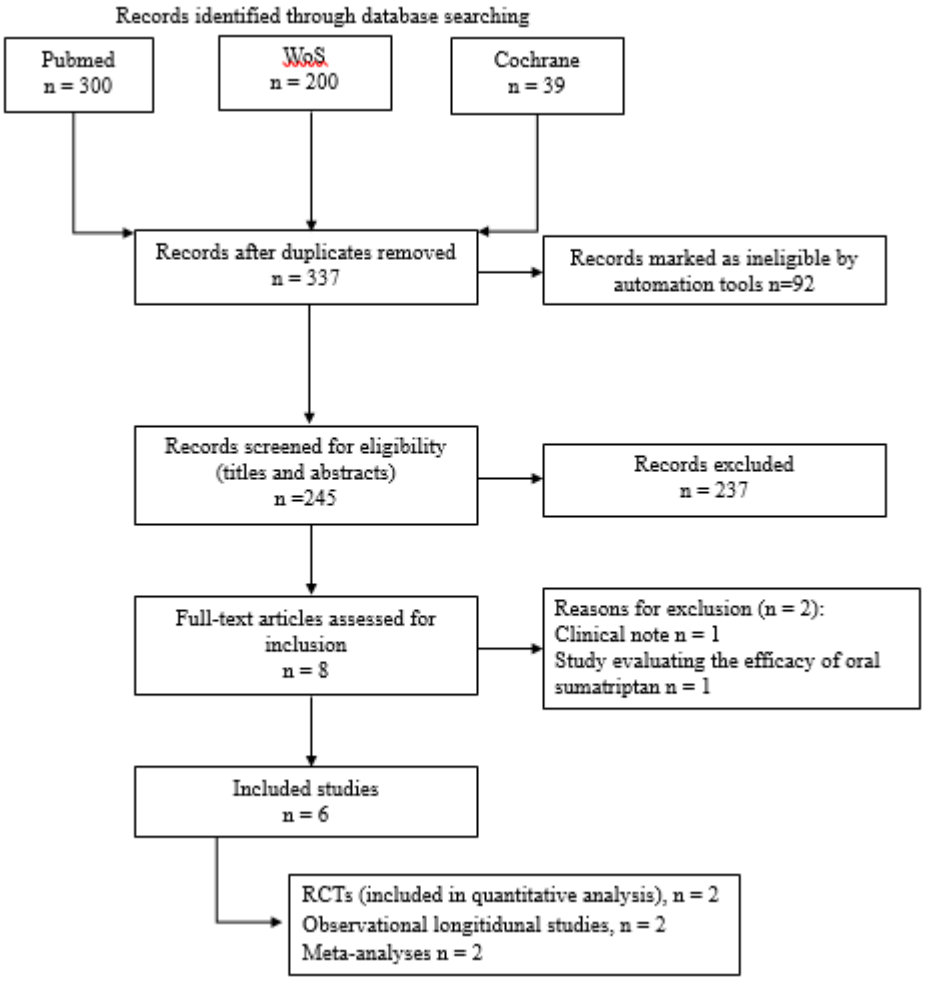
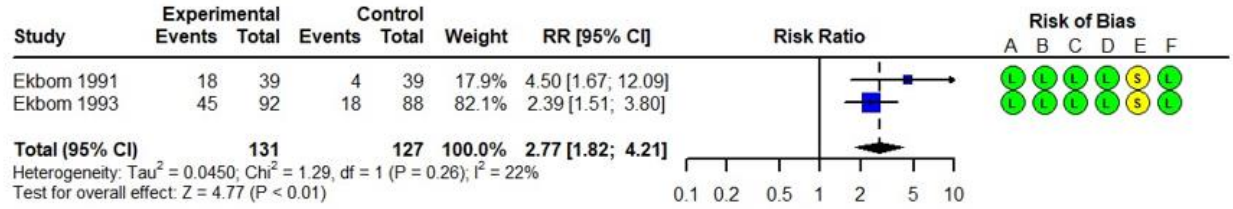


Figure 3 - Flowchart of the literature search of the studies supporting the efficacy of subcutaneous sumatriptan

As regards the comparative analysis of the efficacy of sumatriptan versus other triptans, there are no direct comparative trials, but the Cochrane review by Law et al. *(24)* assesed 2 RCTs studies using the intranasal formulation provided data *(29, 30)*. Both tested 5 mg and 10 mg doses; 117 participants were treated with zolmitriptan 5 mg, 112 with zolmitriptan 10 mg, and 111 with placebo. The proportion of attacks pain-free at 15 minutes with zolmitriptan 5 mg was 8% (9/117; range 2% to 15%). The proportion of attacks pain-free at 15 minutes with placebo was 3% (3/111; range 0% to 6%). The relative benefit of treatment compared with placebo was 2.6 (95% CI 0.80 to 8.5).



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 4. Forest plot showing the comparison between subcutaneous sumatriptan and placebo for pain freedom at 15 minutes in patients with cluster headache attacks

Prednisone/prednisolone

Prednisolone or prednisone is commonly used as a **short-term bridging therapy**, especially when initiating long-term preventive treatments such as verapamil. The review highlighted several studies suggesting that prednisolone/prednisone effectively reduces the frequency and severity of cluster headache attacks in the short term. However, its long-term use is not recommended due to potential adverse effects like adrenal suppression and osteoporosis, underscoring its role as a temporary solution rather than a standalone therapy. The output of our search yielded one RCT vs placebo (Figure 5), which shows that patients in the prednisone group had a mean of 7.1 attacks in the first week compared with 9.5 attacks in the placebo group *(7)*. Furthermore, a single-center retrospective study showed that oral steroids (either prednisone or dexamethasone) were more effective than great occipital nerve (GON) injections; providing benefit in 82.7% of oral steroid encounters and 64.4% of the GON injection encounters *(31)*. Although effective in the short term, prednisolone/prednisone is not suitable for long-term use due to its associated side effects *(32)*. Comparative studies show that while prednisone is effective for immediate symptom relief, it is primarily used as bridging treatment to other treatments rather than as a standalone therapy.

There are no comparative trials comparing the efficacy of prednisolone or prednisone as a bridging therapy in CH.

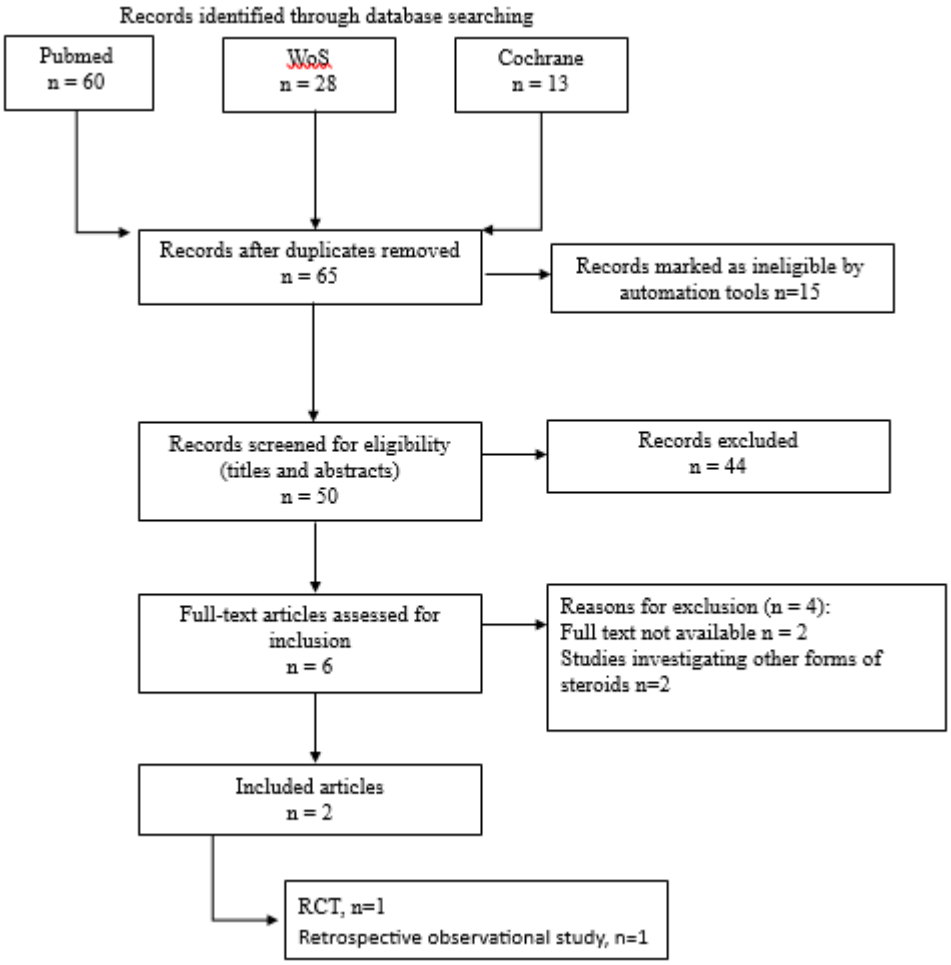


Figure 5 - Flowchart of the literature search of the studies supporting the efficacy of prednisone/prednisolone

Table 1. Studies supporting the efficacy and safety of verapamil, sumatriptan (subcutaneous) and prednisone/prednisolone in managing CH.

Study (First author, year)	Population	Interventions	Outcomes of Interest	Design	Number of Participants
Bussone et al., 1990	Adults with CH	Verapamil vs lithium	Efficacy (attack reduction and side effects)	RCT	24
Leone et al., 2000	Adults with CH	Verapamil vs placebo	Efficacy (attack reduction and side effects)	RCT	30

Meyer et al., 1983	Adults with Migraine and CH	Verapamil, nimodipine and nifedipine	Efficacy (attack reduction and side effects)	Open label study	8 with CH
Blau et al., 2004	Adults with CH	Verapamil	Preventive dosing of the drug	Observational study	70
Gabai et al., 1988	Adults with CH	Verapamil	Efficacy (attack reduction and side effects)	Observational study	48
Lee et al. 2023	Adults with CH	Acute and preventive treatments available in Korea	Efficacy (attack reduction)	Longitudinal observational study	262
Cotton et al., 2023	Adults with CH	Acute and preventive treatments (retrospectively evaluated)	Treatment patterns and drug efficacy	Retrospective survey study	1012
Petersen et al., 2021	Adults with CH	Acute and preventive treatments (retrospectively evaluated)	Efficacy (reduction in attack frequency or intensity)	Cross sectional retrospective study	400
Tuncer Issı et al., 2022	Adults with CH	Acute and preventive treatments (retrospectively evaluated)	Efficacy (attack reduction)	Cross sectional retrospective study	114
Ekbom et al., 1991*	Adults with CH	Sumatriptan sc vs placebo	Efficacy (time to pain relief and side effects)	Crossover RCT	39 (78 attacks)
Ekbom et al., 1993	Adults with CH	Sumatriptan sc 6mg and 12mg vs placebo	Efficacy (time to pain relief and side effects)	Crossover RCT	134 (268 attacks)
Ekbom et al., 1995	Adults with CH	Sumatriptan sc 6mg	Efficacy (time to pain relief and side effects)	Longitudinal observational study	138 (6353 attacks)

Göbel et al., 1998	Adults with CH	Sumatriptan sc 6mg	Efficacy (time to pain relief and side effects)	Longitidunal observational study	52 (2031 attacks)
Obermann et al., 2020	Adults with CH	Prednisone vs placebo	Efficacy (attack reduction and side effects)	RCT	109
Wei et al., 2018	Adults with CH	Oral steroids (either prednisone or dexamethasone or GON block)	Efficacy (attack reduction)	Retrospective observational study	140

**The Sumatriptan Cluster Headache Study Group* CH; Cluster headache, GON; Great occipital nerve, Randomized controlled trial; RCT, sc; Subcutaneous

Table 2. Meta-analyses supporting the efficacy and safety of Verapamil and Sumatriptan (subcutaneous) in managing cluster headaches.

Study (First author, year)	Population	Treatment and comparisons	Outcomes of Interest	Design	Number of studies included for verapamil or sc sumatriptan
Pompilio et al., 2021	Adults with episodic CH	Verapamil, Galcanezumab, Lithium carbonate, Topiramate	Efficacy (attack reduction)	Network meta-analysis	2 (Blau et al. 2004, Gabai et al. 1988)
Law et al., 2013	Adults with acute CH	Sumatriptan, zolmitriptan (vs placebo)	Efficacy (time to pain free and attack reduction)	Systematic review and meta-analysis	2 (Ekbom et al. 1991, Ekbom et al. 1993)
Medrea et al., 2022	Adults with acute CH	Acute treatments (oxygen, sumatriptan, zolmitriptan, niVNS, octreotide) (vs placebo)	Efficacy (time to pain free and attack reduction)	Network meta-analysis	2 (Ekbom et al. 1991, Ekbom et al. 1993)

CH; Cluster headache, VNS; Non-invasive vagal nerve stimulation

Comparative Safety

Verapamil was compared with lithium and placebo, showing higher remission rates and fewer serious adverse events. Verapamil's safety profile is well-documented, with common side effects including gastrointestinal disturbances (e.g., constipation), dizziness, and hypotension, which are generally mild and manageable with dose adjustments *(33, 34)*. However, the most significant safety concern is its cardiovascular impact, particularly bradycardia and atrioventricular (AV) block. Regular ECG monitoring is recommended to detect these issues, especially at higher doses *(35)*. While Verapamil's cardiovascular side effects require monitoring, it remains safer than alternatives like lithium, which carry higher risks of systemic side effects such as renal dysfunction and thyroid abnormalities *(18, 19)*. Verapamil was also commonly associated with side effects, including issues such as constipation, fatigue, abnormal pulse or heart activity, nausea, weight gain, anxiety, and water retention, which led some patients to discontinue the treatment despite its potential effectiveness *(36)*.

In the context of acute management, the safety profile of subcutaneous **sumatriptan** is generally favourable. Across studies, the most commonly reported adverse events were injection site reactions, tingling, and pressure sensations. These side effects are typically transient and well-tolerated *(37)*. However, there is a potential risk of cardiovascular events, particularly in patients with pre-existing cardiovascular conditions, underscoring the importance of careful patient selection and monitoring. Despite these risks, the rapid efficacy of subcutaneous Sumatriptan often outweighs the potential side effects in patients with severe and frequent attacks. In the Cochrane Review by Law et al. *(24)*, the NNH was 6.6 for sumatriptan and 4.6-8.4 (5 and 10 mg dose, respectively) for zolmitriptan. No other data comparing sumatriptan with other acute medications for CH were available.

Prednisone/prednisolone is generally considered safe for short-term use, with common side effects including increased appetite, mood swings, and insomnia. These side effects are well-documented in the literature with common side effects including increased appetite, mood swings, and insomnia *(12, 38)*. However, long-term use is associated with more serious risks, such as adrenal suppression, osteoporosis, and increased susceptibility to infections *(12)*. Seventy-one percent of patients in both groups reported AEs most common were nausea, dizziness, headache, and palpitations *(7)*. Oral prednisone was found to be effective in short-term preventive therapy as a first-line treatment in parallel to the up-titration of verapamil, although the efficacy of prednisone alongside other long-term prevention requires additional investigation.

Key Takeaways

1. **Subcutaneous Sumatriptan**: Its rapid onset and high efficacy in the acute treatment of CH attacks establish it as a critical first-line treatment.

2. **Verapamil**: High-certainty evidence shows that verapamil is effective in reducing attack frequency in cluster headache patients, making it the first choice for preventive care.
3. **Prednisone/prednisolone**: While effective in the short term, its use is limited by its adverse effect profile, making it suitable primarily for short-term bridging therapy.

Assessment of Applicability of the Available Evidence Across Diverse Populations and Settings

In assessing the applicability of the available evidence on the efficacy and safety of **subcutaneous sumatriptan**, **verapamil** and **prednisolone** for the management of cluster headaches, we considered a wide range of patient populations and settings, including demographic diversity, healthcare resources, and comorbid conditions.

Subcutaneous sumatriptan

The effectiveness of subcutaneous sumatriptan in rapidly relieving CH attacks has been established across diverse settings, including high- and low-resource environments. Its fast-acting nature makes it particularly valuable in emergency or outpatient care settings, where immediate relief is critical *(24, 39, 40)*. Studies conducted in both urban and rural healthcare environments have shown that the self-administration of subcutaneous sumatriptan, after proper training, can be a viable option, making it accessible even in under-resourced settings.

While sumatriptan is effective across a broad age range, its applicability in elderly patients and those with cardiovascular comorbidities may require caution. Cardiovascular safety concerns limit its use in patients with pre-existing conditions such as coronary artery disease or uncontrolled hypertension, which may affect its broader applicability in populations with a high prevalence of such conditions *(39)*.

Verapamil

Verapamil is recognized as an effective preventive treatment for CH, with its efficacy primarily established through studies conducted in high-income countries where regular ECG monitoring is feasible. The need for consistent cardiovascular monitoring is critical due to potential side effects such as bradycardia and atrioventricular block, especially at higher doses *(41-43)*. This requirement may limit the generalizability of its use in low- and middle-income countries (LMICs) where such monitoring may not be readily available *(43)*. Despite the monitoring challenges, verapamil's strong efficacy profile and relative affordability make it a valuable option in resource-limited settings for long-term preventive treatment of CH, provided that ECG monitoring can be implemented *(41)*.

In terms of **population diversity**, the majority of studies included male-dominated cohorts, as CH is more prevalent in men. However, the efficacy of verapamil has been consistent across both male and female populations *(43)*. In elderly patients, lower starting doses are recommended due to an increased risk of cardiovascular side effects, highlighting the need for tailored dosage regimens in this population.

Prednisolone/prednisone

Prednisolone or prednisone is typically used as a **short-term bridging therapy** in CH management and has been demonstrated to be effective in **diverse clinical settings** *(44)*. Its affordability and wide availability make it accessible in **low-resource environments**. However, long-term use is not recommended due to its adverse side effect profile, including risks of adrenal suppression, osteoporosis, and increased infection susceptibility, particularly in immunocompromised patients *(45)*.

The evidence for its use in **diverse populations**, including elderly patients and those with multiple comorbidities, suggests that its short-term benefits outweigh the risks when used cautiously. However, in populations with limited access to long-term healthcare follow-up, the risks associated with inadequate monitoring of corticosteroid side effects may limit its broader applicability.

Conclusion

Overall, the applicability of the evidence across diverse populations and settings shows that:

- **Subcutaneous sumatriptan** provides a rapid, effective treatment option for the acute treatment of CH attacks and can be self-administered, making it highly adaptable to diverse healthcare settings, though its use is limited in patients with cardiovascular risks.
- **Verapamil** is a well-supported option for long-term prevention of CH, but its requirement for regular ECG monitoring may limit its use in settings without sufficient healthcare infrastructure.
- **Prednisolone/prednisone** is an accessible and cost-effective short-term option for acute management, but its side-effect profile necessitates careful monitoring, limiting its use to short-term therapy.

Special Circumstances

In the management of CH, certain **special circumstances** may require unique considerations when prescribing and utilizing **subcutaneous sumatriptan**, **verapamil** and **prednisolone**.

These circumstances relate to specific patient populations, comorbidities, or clinical settings where standard treatment protocols may need to be adapted.

Subcutaneous sumatriptan

- **Pregnancy and breastfeeding**: The use of sumatriptan in pregnancy and breastfeeding should be approached cautiously *(46)*. While limited data suggest that sumatriptan can be used during pregnancy when the benefits outweigh the risks, it is typically reserved for **special circumstances** where no alternatives are available, and the severity of cluster headaches necessitates immediate intervention. Sumatriptan is excreted in breast milk, so mothers should be advised to pump and discard milk for a period after taking the drug, particularly if repeated doses are required.
- **Cardiovascular risk factors**: In patients with known cardiovascular risks, including hypertension, atherosclerosis, or a history of myocardial infarction, sumatriptan should be avoided or used with extreme caution *(47)*. In **emergency settings** where rapid intervention is required and cardiovascular risks have been evaluated, sumatriptan may be used under close clinical supervision.

Verapamil

- **Cardiovascular comorbidities**: In patients with pre-existing cardiovascular diseases, such as heart failure or arrhythmias, the use of verapamil must be carefully monitored. Verapamil's propensity to cause bradycardia or atrioventricular block, particularly at higher doses, requires regular ECG monitoring *(48)*. For patients in settings where frequent monitoring is not feasible, careful dose management with lower starting doses should be considered. Special caution is advised in elderly patients, as they are more susceptible to cardiovascular side effects *(48)*.
- **Pediatric Use**: While CH is rare in children, verapamil has been used cautiously in pediatric patients in **special cases** *(49)*. Due to a lack of robust data on its use in children, pediatric dosing and long-term safety remain areas requiring more research. For children experiencing severe CH attacks, the dose must be adjusted based on body weight and clinical response, with close monitoring of cardiovascular function *(50)*.
- **Pregnancy:** Existing data on the use of verapamil in pregnant women primarily come from observational studies and case reports rather than randomized controlled trials, due to ethical considerations. However, the available evidence suggests that Verapamil does not significantly increase the risk of congenital malformations or adverse pregnancy outcomes. In a large cohort study, verapamil use during the first trimester was not associated with an increased risk of major birth defects compared to non-exposed pregnancies. Verapamil is classified as a Category C drug by the FDA for use during pregnancy. This category indicates that animal reproduction studies have

shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans. However, potential benefits may warrant the use of the drug in pregnant women despite potential risks. Animal studies have demonstrated that verapamil crosses the placental barrier. Teratogenic effects (birth defects) have not been consistently observed, but some studies have shown embryotoxicity (harm to the embryo), particularly at high doses. A review of 39 pregnancies exposed to verapamil reported no significant increase in adverse fetal outcomes, with only isolated cases of transient neonatal hypotension observed, which were managed successfully without long-term effects *(51)*. Additionally, Briggs et al. *(52)* concluded that verapamil does not have teratogenic effects and is considered relatively safe for use during pregnancy when the benefits outweigh the potential risks. It is also important to note that verapamil is not an enzyme inducer, reducing the risk of drug-drug interactions, which is beneficial for pregnant women who may require concurrent medications. Overall, while verapamil should be used during pregnancy only when clearly needed, current evidence supports its relative safety in this population, offering an effective treatment option for pregnant women suffering from cluster headaches.

- **Elderly people:** Verapamil is effective in reducing the frequency and severity of CH attacks in patients over the age of 65. In clinical trials, 80% of older patients reported at least a 50% reduction in the frequency of headache attacks *(34)*. Importantly, Verapamil exhibits a favourable safety profile in this demographic. Only 15% of older adults experienced adverse events significant enough to lead to discontinuation of the medication. These adverse events were generally mild and included constipation, dizziness, and hypotension *(16, 18)*. Notably, verapamil is not an enzyme-inducing drug, which reduces the risk of drug-drug interactions—a crucial consideration for older adults who are often on multiple medications (polypharmacy). This characteristic minimizes potential complications arising from polypharmacy, thereby enhancing its safety profile. Additionally, unlike some other treatments for CH, verapamil does not negatively impact bone health or exacerbate cardiovascular issues, which are common concerns in the elderly population *(8)*. Overall, the evidence supports the use of verapamil as a safe and effective treatment for cluster headaches in older patients, offering a well-tolerated option with a low incidence of severe side effects *(53)*. Brand et al discusses the use of verapamil in the pharmacotherapy for CH, highlighting its possible cardiac side effects and recommending an electrocardiogram (ECG) before treatment with verapamil, particularly in elderly individuals *(41)*.

Prednisolone/prednisone

- **Immunocompromised patients**: In patients who are immunocompromised, such as those with HIV/AIDS or on immunosuppressive therapy, the short-term use of prednisolone can pose risks of infections, delayed wound healing, or exacerbation of

latent infections. Careful risk-benefit analysis should be undertaken, and alternatives should be considered in such **special circumstances**.

- **Patients with diabetes**: Corticosteroids, including prednisolone, can exacerbate hyperglycemia, making its use problematic in patients with diabetes or those at high risk for metabolic syndrome *(54)*. In these patients, alternative short-term bridging therapies should be considered, or blood sugar levels should be closely monitored, with appropriate adjustments made to diabetes medications.
- **Bone health concerns**: In populations at risk for osteoporosis, including postmenopausal women or patients with long-term corticosteroid exposure, even short courses of prednisolone can contribute to bone loss. In these **special circumstances**, the use of bone protective agents, such as calcium and vitamin D supplementation or bisphosphonates, may be considered to mitigate the risk.

Low-Resource Settings

Verapamil

- For patients without access to ECG monitoring, lower doses of verapamil with gradual titration and close clinical monitoring may be considered. Education on symptom recognition for bradycardia or hypotension should be provided to patients and caregivers.

Conclusion

The management of CH often requires adaptation to **special circumstances** such as pregnancy, cardiovascular comorbidities, pediatric and adolescent use, immunocompromised states, and limited access to healthcare resources. In these cases, individualized treatment plans should be developed, balancing efficacy with the specific needs and risks of the patient.

REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE OF COMPARATIVE SAFETY

Sumatriptan

Subcutaneous sumatriptan is known for its rapid efficacy in treating acute cluster headache attacks. However, its safety profile must be carefully managed, particularly in patients with underlying cardiovascular conditions. Study mentions several side effects associated with sumatriptan use, particularly **subcutaneous administration**. These include **local injection site reactions**, **chest symptoms** (typically mild or moderate, of short duration, and resolving

spontaneously), and **nausea** *(12, 24)*. These effects are generally mild and self-limiting but warrant careful monitoring in patients with a history of cardiovascular disease *(12)*.

Sumatriptan's most serious safety concern is its potential to cause vasoconstriction, which can lead to coronary artery vasospasm, myocardial infarction, or stroke in susceptible patients. For this reason, it is contraindicated in patients with a history of ischemic heart disease, uncontrolled hypertension, or cerebrovascular disease *(55)*. Despite these risks, sumatriptan remains a critical option for rapid relief in acute cluster headache scenarios due to its superior efficacy compared to other acute treatments like oral triptans or oxygen therapy *(55)*.

Verapamil

Verapamil is widely used for the prevention of cluster headaches, and while it is generally well-tolerated, it carries specific risks that need to be considered. According to EAN guidelines, the side effects of verapamil mentioned include ECG abnormalities, such as heart block and bradycardia *(12)*. Regular ECG monitoring is recommended, especially at higher doses, to prevent these potentially serious cardiac complications. The most common adverse effects associated with verapamil include gastrointestinal disturbances such as constipation, as well as dizziness, fatigue, and headache. In more serious cases, cardiovascular effects, particularly bradycardia and atrioventricular (AV) block, have been reported *(16)*. A meta-analysis of randomized controlled trials identified an incidence rate of 1-2% for significant bradycardia and AV block in patients treated with verapamil, especially at higher therapeutic doses *(35)*.

Verapamil's use is also associated with hypotension, especially in elderly patients, which necessitates cautious dose titration and regular blood pressure monitoring *(33)*. Additionally, verapamil can exacerbate pre-existing heart failure in patients with reduced ejection fractions, making its use in this population particularly challenging *(56)*. However, compared to other prophylactic agents like lithium, verapamil has a more favourable side effect profile and superior tolerability, leading to its recommendation as the first-line preventive treatment for cluster headaches *(19)*.

Prednisolone/prednisone

Prednisolone or prednisone is typically used as a short-term bridging therapy for cluster headache, allowing time for long-term preventive treatments to take effect. While effective, its use is limited by its side effect profile, particularly during prolonged therapy. The most common short-term side effects include increased appetite, weight gain, insomnia, and mood changes. Longer-term use is associated with more serious adverse effects, including adrenal suppression, osteoporosis, hypertension, and increased risk of infections *(57)*.

When used for short durations, its safety profile is generally acceptable, but clinicians must carefully monitor patients for signs of corticosteroid-related toxicity. In elderly patients, the risks of osteoporosis and hypertension are heightened, necessitating the use of lower starting doses and regular monitoring *(58)*.

Key Messages on Comparative Safety

- **Sumatriptan (Subcutaneous)**: Offers rapid relief but carries a significant risk of cardiovascular side effects in susceptible patients. Contraindicated in patients with ischemic heart disease and uncontrolled hypertension.
- **Verapamil**: While generally well-tolerated, verapamil's cardiovascular risks, particularly bradycardia and AV block, warrant regular ECG monitoring. Compared to lithium, verapamil has a superior safety profile, particularly in terms of gastrointestinal side effects.
- **Prednisolone**: Effective for short-term use, but carries serious risks with prolonged use, including adrenal suppression and osteoporosis. Short-term therapy minimizes these risks, but careful monitoring is necessary, particularly in elderly patients.

Considering these safety profiles, sumatriptan, verapamil and prednisolone remain essential treatments in cluster headache management, provided that proper patient selection and monitoring are employed to mitigate risks.

Section 9: Summary of recommendations in current clinical guidelines

There are no recommendations for the treatment of CH in the current WHO guidelines. In 2007 Lifting The Burden in collaboration with the European Headache Federation and WHO published 'Aids for management of common headache disorders in primary care' in collaboration *(59)*. Within this document, sumatriptan 6 mg subcutaneously is described as 'the only proven highly effective acute treatment' for CH. For prevention, verapamil 240-960 mg daily and prednisolone 60-80 mg od for 2-4 days and discontinued by dose reduction over 2-3 weeks, are both recommended. Verapamil is widely recognized and recommended by various other prominent organizations for its effectiveness in cluster headache management.

Recommendations in other current clinical guidelines

Recent guidelines from global clinical authorities have already recognized verapamil, sumatriptan (subcutaneous), and prednisolone or prednisone as key treatments for cluster headaches:

TOP Primary care management of headache in adults *(60)*	2016	• Subcutaneous sumatriptan 6 mg is an effective option for the acute treatment of cluster headache attacks • For prevention Verapamil 240 to 480 mg is recommended as the drug of first choice • Prednisolone 60 mg for five days, then reduced by 10 mg every two days until discontinued is recommended as transitional therapy used to stop the attacks while prevention is being established
British Association for the Study of Headache (BASH) Guidelines *(61)*	2019	• The most effective acute treatment is sumatriptan 6mg subcutaneous injection with significant relief within 15 minutes • Verapamil is an effective preventive treatment in cluster headache • Oral corticosteroids have been shown to be effective in the prevention of cluster headache attacks
Japanese Headache Society Guidelines *(62)*	2019	• For acute treatment subcutaneous injection of sumatriptan 3 mg (up to 6 mg/day) is recommended • For prevention Verapamil 360 mg/day has been shown overseas to have prophylactic effect

		• Corticosteroids are considered effective, but there is no clear evidence
Danish Headache Society Guidelines *(63)*	2021	• Subcutaneous injection of sumatriptan 6 mg is considered 1st line treatment if oxygen is insufficient or if the patients need a treatment more easily handled when not at home • Verapamil is the first-line preventive treatment of cluster headache. • Glucocorticoids can be used in transition phases to achieve a quick relief before the effect of other preventive treatment is sufficient or if patients have a very short bout: Prednisone tablets 75 mg once a day for 5 days hereafter reducing the dose with 12.5 mg a day, is […] a very efficient treatment.
European Academy of Neurology Guidelines *(12)*	2023	• Subcutaneous sumatriptan 6 mg: First choice in the acute treatment of the attack. Level of evidence: low; Strength of recommendation: strong. • Verapamil: it is the medication of choice for the prevention of episodic and chronic cluster headaches. Initial dose of 80 mg oral (1–1–1) daily, up to target dosage of 360 mg/day. Can be increased to 720 mg/day or higher with monitoring for side effects (blood pressure and ECG) • Efficacy reached depending on dosage after 2–3 weeks. Prednisone can be added to bridge time until efficacy reached. Level of evidence: consensus, Strength of recommendation: consensus. • Prednisone: Indicated to bridge until verapamil is efficacious. Initial dose 250 or 500 mg iv in the morning or 60–100 mg po for 5 days, followed by reductions of 10 mg every 4 days, or equivalent. Gastric protection required. Avoid prolonged treatment regimes. Strength of evidence: low; Strength of recommendation: weak.
American Headache Society *(64)*	2019	• Sumatriptan is recognized as the most effective acute treatment for CH. The guidelines recommend subcutaneous administration of sumatriptan 6 mg. Sumatriptan is preferable to other acute treatments, including oxygen therapy, due to its consistent effectiveness in reducing the intensity and duration of cluster headaches.

		• Verapamil is recommended as the first line primary preventive treatment suggesting an initial dosage of 240 mg/day, with the possibility of titrating up to 960 mg/day. • Prednisone is recommended for short-term use as a bridging therapy. The guidelines advise an initial dose of 60-80 mg daily for 2-4 days, followed by a gradual taper over 2-3 weeks.
UK National Institute for Health and Care Excellence (NICE) *(65)*	2022	• **Sumatriptan** subcutaneous at a dose of 6 mg is recommended as the most effective treatment for acute CH attacks. Subcutaneous sumatriptan is superior to oral or intranasal sumatriptan because of its faster bioavailability and more immediate effects. • **Verapamil** is recommended as a first-line prophylactic treatment for CH, with a gradual dose escalation approach from an initial dose of 240 mg/day and potentially increasing up to 960 mg/day, based on the patient's response and tolerance. • **Prednisolone** at an initial dosage of 60-80 mg daily for 2-4 days, followed by a gradual taper over 2-3 weeks is recommended as a short-term preventive treatment option for CH, particularly in bridging therapy.
European Academy of Neurology (EAN) *(12)*	2023	• **Sumatriptan**, particularly in its subcutaneous 6 mg form, is identified as the most effective acute treatment for CH. • Prednisone is recommended for short-term prevention of cluster headaches, particularly during the transitional phase when initiating or adjusting long-term preventive therapies like Verapamil. • Verapamil, at an initial dose of 240 mg/day, with the potential to titrate up to 960 mg/day, depending on patient response and tolerance, is strongly recommended as the first-line preventive treatment for CH, particularly in the chronic type.

Section 10: Summary of available data on comparative cost and cost-effectiveness

The literature is unhelpful: there are no economic studies of any of these medications for the treatment or prevention of cluster headache.

Sumatriptan (6 mg subcutaneous injection)

Acute treatment with sumatriptan is compared with no treatment. The **subcutaneous** formulation is highly effective and has a rapid onset of action, reducing time spent in the ictal state by up to 80% (see section 8). The only alternative acute treatment is high-concentration inhaled oxygen; this is not considered in view of the very substantial logistic obstacles to its storage and distribution in low- and middle-income countries).

Cost/HLY gained

Sumatriptan injection is not widely available. We asked experts in nine countries ranging from low to higher-middle income for local prices, but only two could supply them: Brazil (US$ 12.63) and Argentina (US$ 40.86) (prices converted from local currencies at current exchange rates). Instead, we used the price in the UK NHS drug tariff (US$ 31.81), which fell between these.

To calculate cost/HLY gained for sumatriptan, we assumed one dose per attack, administered immediately upon the onset of symptoms. We took the duration of untreated attacks (D) from Dodick 2000 as 45-90 minutes (mean 67.5 minutes. We assumed D would be reduced to 15 minutes with probability (P) of 63/131 (48.1%) established from two clinical trial (Ekbom 1991; Ekbom 1993). These data are summarised in Table 1.

Table 1. Summary of data on sumatriptan for economic analysis

	Cost per injection (US$ 2024 values)	D = mean attack duration (minutes)	Pr = proportion of those treated who respond (D reduced to 15 minutes)
Sumatriptan (6 mg subcutaneous injection single dose)	15.134	45-90 (say 67.5)	0.481

We calculated HLYs gained per treatment using the formula:

[(D–15)/(60*24*365)]*DW*P

Since the acute attack is totally disabling with excruciating pain, we assumed a disability weight (DW) of 1 for the ictal state. Thus, cost/HLY gained is:

31.81/{[(67.5-15)/(60*24*365)]*1*0.481} = US$ 662,086.

On this evidence, sumatriptan 6 mg subcutaneously is not cost-effective. However, during cluster periods, the interictal burden is very high: most patients are unable to function usefully because of frequent disruption by very intense pain coupled with interrupted sleep (many attacks are nocturnal, waking the patient who is unable to remain in bed). We applied a DW of 0.5 for this period, and, accordingly, discounted the DW for the ictal episode to 0.5 (1-0.5). We took cluster period duration (Dep) from Dodick 2000 as 42-84 days (mean 63 days) and mean attack frequency during cluster periods (F) from Goadsby 2019 as 2.5/day. We used the same assumptions regarding treatment as above.

Accordingly, we calculated HLYs gained per episode using the formula:

{[(D–15)/(60*24*365)]}*DW*P*2.5*63}

and cost/HLY gained per episode as:

Thus, cost/HLY gained is:

(31.81*2.5*63)/{{[(67.5-15)/(60*24*365)]*0.5*0.481} + [(63/365)*0.5*0.481]} = US$ 120,623.

On this evidence, sumatriptan 6 mg subcutaneously is still not cost-effective at this price. However, there is no patent protection, and the price is likely to drop substantially if demand increases through addition to the EML, since there are no viable alternatives. Applying the current price for Brazil rather than that for UK, cost/HLY gained is:

(12.63*2.5*63)/{{[(67.5-15)/(60*24*365)]*0.5*0.481} + [(63/365)*0.5*0.481]} = US$ 47,892.

Prednisolone and verapamil for prevention

We compared these two preventative interventions with no treatment, since there are no satisfactory alternatives. Lithium is effective but necessitates regular blood-level monitoring, which is often unfeasible in low- and middle-income countries (LMICs). Prednisolone is already included on EML for other indications. Its short-term use often provides effective results either immediately or within three days.

We used the same assumptions as above, and a timeframe of 1 year, with the further assumption (based on expert opinion) of a mean of two cluster periods during the year. We also assumed (conservatively) that treatment reduced cluster period duration, not attack frequency within cluster periods or cluster period frequency. We assumed adherence to be 100% given the severity of CH.

We calculated healthy life years (HLYs) gained per treated individual per year using the formula:

HLYs/person/year gained = (mean TIS untreated – mean TIS treated) * DW

where TIS in years/year is the total time per year spent in the ictal state and DW (for the ictal state) = 1.

TIS untreated is the product of cluster period frequency per year, cluster period duration (in days), attack frequency per day during cluster periods, and attack duration (in years). TIS treated is calculated similarly but with reduced cluster period duration.

The available efficacy data were poor. It should be acknowledged that placebo-controlled trials in CH are ethically very difficult.

Verapamil (80 mg tablets) for prevention

We modelled verapamil as a long-term therapy, applying a stopping rule that treatment would be discontinued at the expected end of the cluster period. While cluster period duration is variable, we used a mean of 63 days (see above). Thus treatment would be taken on a total of 126 days/year. We assumed a mean daily dosage of 360 mg (4.5*80 mg), recognising that titration was necessary, upwards from 120 mg, with a target dosage in the range 240-480 mg, but usually at the upper end of this. We obtained prices of verapamil 80 mg tablets from experts in nine countries (Egypt, Georgia, Moldova, Nepal, India, Indonesia, Mongolia, Argentina and Brazil), and from the UK NHS drug tariff, which were in the range US$ 0.012 to US$ 0.495, with a median of US$ 0.071.

We assumed two ECGs would be needed during each treated cluster period (4/year). We obtained costs per ECG from experts in Moldova, Mongolia, Argentina and UK, in the range US$ 2.96 to US$ 49.20, with a median of US$ 14.29.

Thus, treatment-associated costs/person/year = US$ [(0.071*4.5*126)+(4*14.29)] = US$ 97.42.

We took efficacy data from a single study of N=70 (Blau et al, 2004). This reported a reduction in cluster period duration of 56 days in 36/70, 49 days in 11/70 and 0 days in 23/70 (weighted mean 36.5 days).

Therefore:

HLYs/person/year gained = (2*36.5*2.5*67.5/[60*24*365*1]) = 0.0234;

cost/HLY gained = US$ 97.42/0.0234 = US$ 4,163.

On this evidence, verapamil is cost-effective in CH prevention.

It should be noted that this analysis did not take account of interictal lost health, which is expected to be averted by reduction in duration of cluster periods. This loss is substantial (see above, in sumatriptan analysis).

Prednisolone (5 mg tablets) as bridging therapy for prevention

We made the same general assumptions.

We obtained prices of prednisolone (or prednisone) 5 mg tablets from experts in seven countries (Egypt, Georgia, Moldova, Nepal, Indonesia, Mongolia and Brazil), and from the UK NHS drug tariff, which were in a range of US$ 0.013 to US$ 0.133, with a median of US$ 0.053.

The only efficacy data was from a single placebo-controlled trial of N=109 (Obermann et al, 2020). This study used a starting dosage of 100 mg prednisone for 5 days, tapering by 20 mg every 3 days over 17 days and reported a mean reduction by 2.4 attacks in the first week in the prednisone group compared with the placebo group.

We calculated the treatment costs relevant to this study (per cluster period) as:

[(20*5)+(16*3)+(12*3)+(8*3)+(4*3)]*0.053 = US$ 11.66

and HLYs/person gained as:

(2.4*67.5/[60*24*365*1]) = 0.000308.

Therefore:

cost/HLY gained = US$ 11.66/0.000308 = US$ 37,875.

On this evidence, prednisolone may not be cost-effective. However, clinical experience is that a worthwhile proportion of patients respond rapidly (within 3 days) with complete attack cessation. In these, assuming verapamil was initiated simultaneously (with mean response to that drug of a reduction of 36.5 days in cluster period duration from 63 days to 26.5 days) there would be a further mean reduction of 23.5 days in cluster period duration attributable to prednisolone. In these patients:

HLYs/person/year gained are:

(2*23.5*2.5*67.5/[60*24*365*1]) = 0.0151

cost/HLY gained = US$ (2*11.66)/0.0151 = US$ 1,544.

On this analysis, prednisolone may be cost-effective with a stopping rule applied: used in all patients initially, but repeated in subsequent cluster periods only in those responding well in the first.

It should be noted again that this analysis did not take account of interictal lost health, which is expected to be averted by reduction in duration of cluster periods.

Section 11: Regulatory status, market availability and pharmacopoeial standards

Subcutaneous sumatriptan

Regulatory Status:

Subcutaneous sumatriptan is approved by various regulatory agencies, including the **FDA**, **EMA**, and **Health Canada**, primarily for the **acute treatment of cluster headaches** and migraines. Initially approved in the early 1990s, it is recognized for its rapid onset of action, which makes it a first-line therapy for cluster headaches. It is approved in injectable form, often supplied in **pre-filled syringes or auto-injectors**.

Market Availability:

Subcutaneous sumatriptan is widely available across the world, marketed under brand names such **as Imigran**, **Imitrex** and **Zembrace SymTouch**, alongside various generic formulations. The availability of generic versions has made the treatment more accessible, particularly in regions with limited healthcare resources. Subcutaneous formulations are available in **North America, Europe, Asia, and parts of Latin America and Africa**, and they are designed for **self-administration** by patients, enhancing their usability in diverse healthcare settings.

Verapamil

Regulatory Status:

Verapamil is widely approved by regulatory agencies in many regions, including the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada, Australia's Therapeutic Goods Administration (TGA), and Japan's Pharmaceuticals and Medical Devices Agency (PMDA). It is commonly indicated for the treatment of cardiovascular conditions such as hypertension, angina, and arrhythmias. While its use for the prophylaxis of cluster headaches is not a formally approved indication in many regions, it is widely recognized as an off-label use. Verapamil is a Category C drug for pregnancy according to the FDA, indicating potential risks based on animal studies, but it may still be used in pregnant women when the benefits outweigh the risks. It is available only by prescription worldwide, reflecting the need for medical supervision, particularly given its cardiovascular effects.

Market Availability:

Verapamil is available globally in multiple formulations, including immediate-release and extended-release tablets, as well as injectable solutions. The wide availability of **generic versions** has made Verapamil a cost-effective option for long-term treatment. It is particularly accessible in high-income countries but is also available in many low- and middle-income countries. Verapamil remains a prescription-only drug in all regions, requiring physician oversight to manage its administration and potential side effects, particularly the need for **ECG monitoring**.

Prednisolone/prednisone

Regulatory Status:

Prednisone or prednisolone is approved for a wide range of conditions by regulatory bodies such as the **FDA** and **EMA**, including autoimmune and inflammatory diseases. While its use in cluster headaches is **off-label**, it is frequently used in clinical practice as a **bridging therapy** during cluster periods. Regulatory agencies approve its use in various strengths and formulations, making it a versatile treatment option for multiple conditions.

Market Availability:

Prednisone or prednisolone is widely available globally, with numerous manufacturers offering it under both branded and generic names (e.g., **Deltasone**, **Rayos**). It is a relatively inexpensive drug and is widely used across healthcare systems in both high-income and low-income countries. Prednisone is typically prescribed in **tablet form**, with various dosages available (e.g., 1 mg, 5 mg, 10 mg, 20 mg), offering significant flexibility in treatment regimens.

Pharmacopoeial Standards

Subcutaneous Sumatriptan

Sumatriptan is included in major pharmacopoeias, which provide detailed standards for **purity**, **strength**, and **stability**.

- **United** States Pharmacopoeia (USP): https://www.uspnf.com/errata/sumatriptan-2019-06-01

- **European Pharmacopoeia (Ph. Eur.):** https://www.ema.europa.eu/en/medicines/psusa/psusa-00002832-201909
- **Japanese Pharmacopoeia (JP):** https://ss.pmda.go.jp/en_all/search.x?q=subcutaneous+sumatriptan&x=0&y=0&ie=utf8&page=1&pagemax=10&imgsize=1&pdf=ok&zoom=1&page=1&suggest=1&counsel=1&ref=www.pmda.go.jp&pid=KCwXLniapEyCNfYLZqjtiQ..&qid=18eqo_MrC04EBIsYpqx7-s1urpxWQ7z5

Verapamil

Verapamil hydrochloride is included in several major pharmacopoeias.

- **United States Pharmacopoeia (USP)**: https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/verapamil_hcl_er_tabs.pdf
- European Pharmacopoeia (Ph. Eur.): https://www.ema.europa.eu/en/documents/psusa/verapamil-cmdh-scientific-conclusions-and-grounds-variation-amendments-product-information-and-timetable-implementation-psusa00003105202001_en.pdf
- Japanese Pharmacopoeia (JP): https://ss.pmda.go.jp/en_all/search.x?nccharset=CE0EC294&nccharset=FEF28A70&q=verapamil&ie=UTF-8&page=1

Prednisolone/prednisone

Prednisone is also included in major pharmacopoeias.

- United States Pharmacopoeia (USP): https://www.uspnf.com/errata/prednisolone-sodium-phosphate-2019-04-01
- European Pharmacopoeia (Ph. Eur.): https://www.ema.europa.eu/en/medicines/psusa/psusa-00002506-202308

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