This site is intended for healthcare professionals

Edition: [ENGLISH](https://www.medscape.com) [DEUTSCH](http://deutsch.medscape.com) [ESPAÑOL](http://espanol.medscape.com) [FRANÇAIS](http://francais.medscape.com) [PORTUGUÊS](http://portugues.medscape.com)

[Dr. M Togha](https://www.medscape.com/viewarticle/918806?nlid=132208_405&src=WNL_mdplsfeat_191022_mscpedit_neur&uac=75644CY&spon=26&impID=2139956&faf=1)

Top of Form



Bottom of Form

Top of Form

Bottom of Form

[](https://www.medscape.com/)

[News & Perspective](https://www.medscape.com) [Drugs & Diseases](https://reference.medscape.com) [CME & Education](https://www.medscape.org) [Academy](https://www.medscape.com/academy/business) [Consult](https://www.medscape.com/consult) [Video](https://www.medscape.com/video)

[Headache](http://www.medscape.com/viewpublication/1007)

**Verapamil and Cluster Headache: Still a Mystery**

**A Narrative Review of Efficacy, Mechanisms and Perspectives**

Anja S. Petersen, MD; Mads C. J. Barloese, MD, PhD; Agneta Snoer, MD; Anne Mette S. Soerensen, MD; Rigmor H. Jensen, MD, DMSc

[Disclosures](javascript:showModal('authordisclosures');)

Headache. 2019;59(8):1198-1211.

* ADDED TO EMAIL ALERTS

**Abstract and Introduction**

**Abstract**

**Objective:** A evaluation of the effect of verapamil and other calcium channel blockers in cluster headache (CH) treatment and an investigation of possible effect mechanisms.

**Background:** Verapamil has been used in the prevention of CH for almost 3 decades, however, the mode of action and therapeutic target is still unknown.

**Methods:** A Pubmed search was conducted: "Verapamil"[Mesh] and "Cluster Headache"[Mesh]. We identified 5 relevant studies for CH. Publications were included if they made a substantial contribution within 3 prespecified areas: Efficacy (randomized controlled-trials or open labels studies), safety, and mechanism of effect.

**Results:** *Clinical effect*: Clinical preventive treatment of CH with verapamil is based on 2 randomized controlled studies and 3 open-label studies. In total, 183 CH patients participated. Verapamil 360 mg/day was used in both controlled studies. Half of the chronic patients experienced benefit from verapamil treatment and the attack burden of episodic patients was, on average, reduced by 1 attack/day. Open-label studies support a dose-dependent level of efficacy. *Mechanism of effect*: Human and animal studies indicate that verapamil may exert its effect by modulating circadian rhythms, perhaps in central pacemakers, and/or by affecting release of calcitonin gene-related peptide.

**Conclusion:** Verapamil appears to be an effective prophylactic drug in the treatment of CH and despite the scarcity of controlled trials, it is still the drug of choice. A chronotherapeutic approach might increase the effect. More basic and pharmacokinetic research is needed before the mechanism can be fully understood.

**Introduction**

Verapamil is the first line treatment in the prevention of cluster headache (CH) attacks.[[1](javascript:void(0);)] Discovered by the German physiologist Fleckenstein in the mid-1960s,[[2](javascript:void(0);)] it was developed because of the vasodilatory effect, and along with other calcium channel blockers (CCB) it was widely used to treat cardiovascular diseases. CH is a primary headache with severe unilateral pain of which the majority of the patients experience bouts separated by pain-free periods.[[3](javascript:void(0);),[4](javascript:void(0);)] The waxing and waning of episodic CH (eCH) create some difficulty in designing and completing trials of preventive therapy. Thus, there are no large scale randomized controlled trials (RCT) of verapamil's effect in the treatment of CH and prevention of CH attacks is still an off-label use of verapamil. However, in addition to the reviewed studies, verapamil has been field tested by headache specialists all over the world and our clinical experience is that most patients are satisfied with this treatment.

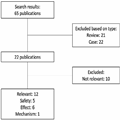
Migraine and CH treatment with CCBs began in the early 1980s based on the assumption that CCB could prevent vasospasms and abolish possible painful vasodilation.[[5](javascript:void(0);)] Decades have passed since verapamil was introduced and vasospasms are no longer believed to be a generator of CH attacks. However, verapamil's mode of action in CH is unknown[[6](javascript:void(0);)] and understanding the mechanism of action might also elucidate the CH pathophysiology.

There are no currently available reviews of verapamil with a focus on efficacy and mechanism of action. Existing reviews focus on treatment of CH in general and 1 review compares verapamil therapy in a cardiological and neurological context and critically evaluates the mode of action.[[6](javascript:void(0);)] However, this review does not propose new hypothesis on mechanism of effect.

The aim of this review is to conduct a narrative evaluation of the effect of verapamil and other CCBs in CH treatment and an investigation of possible effect mechanisms. Based on our results, we aim to propose new perspectives for optimizing and/or personalizing treatment with verapamil.

### Method

We searched the Pubmed database using the search line "Verapamil"[Mesh] and "Cluster Headache"[Mesh] in September 2018 (Figure 1). Only manuscripts in English were included. We applied no time limits. We included relevant manuscripts from the reference lists of included publications. Manuscripts had to include a substantial contribution in 3 prespecified areas: Effect, safety, or mechanism of effect. Data were not extracted for a meta-analysis. For each relevant study of effect, we applied the PICO analysis.[[7](javascript:void(0);)] Risk of bias was analyzed using elements from the Cochrane Risk of Bias Tool.[[8](javascript:void(0);)] Only RCTs and open-label studies of CCBs in CH (diagnosed according to the criteria of the International Headache Society if available at the time point) were included in the analysis. Post hoc search lines were carried out regarding other calcium blockers eg. "Nimodipine"[Mesh] AND "Cluster Headache"[Mesh]. Publications highlighting mechanism of action in central nervous system disorders were included. Effect measurements are stated as in the original articles. Investigation of interactions was done using "[www.interaktionsdatabasen.dk](http://www.interaktionsdatabasen.dk)" which is a website provided and maintained by the Danish Medicine Agency.[[9](javascript:void(0);)] Rationale, hypothesis and planned methods were decided before the review process, however, no review protocol was uploaded at PROSPERO. P values under .05 were considered significant.

[](javascript:showModal('918806-fig1');)

[(Enlarge Image)](javascript:showModal('918806-fig1');)

**Figure 1.**

Flow chart of search. Search line (pubmed database): "Verapamil"[Mesh] and "Cluster Headache"[Mesh]; September 2018. Papers deemed relevant had to include a substantial contribution in 3 prespecified areas: Effect (randomized controlled trials or open-label studies), safety, or mechanism of effect. Otherwise papers were deemed not relevant.

### Results

**Verapamil.**The first study to suggest a therapeutic advantage using CCBs in CH patients was published in 1983.[[5](javascript:void(0);)] The study included both the migraine and the CH patients and evaluated the effect of nimodipine, nifedipine, and verapamil. The verapamil sub-study was an open-label design that included chronic CH (cCH) patients, who were not CCB-naive. According to the authors, during treatment with verapamil, all 5 patients experienced reduced headache frequency with no further description. The dosage used ranged between 160 and 720 mg (mean 240 mg/day). Given the small sample size and study design, the study was only hypothesis generating. It was succeeded by another open-label study by Gabai et al[[10](javascript:void(0);)] published in 1989 including 48 CH patients (33 eCH and 15 cCH). Sustained release verapamil was initiated at 120 mg twice daily and increased until efficacy or intolerable side effects. Improvement was obtained after an average of 1.7 weeks (range: 1–6 weeks) in eCH patients and after 5 weeks (range: 1–20 weeks) in cCH patients. Sixty-nine percent reported more than a 75% reduction in headache frequency and only 9 CH patients did not benefit (<25% frequency reduction). Among the episodic patients, 24 of 33 (75%) improved >75%, but only 9 of 15 (60%) responded equally as well in the chronic group. Three patients discontinued due to side effects. Chronic patients needed a higher dosage of verapamil compared to eCH patients (mean 572 vs 354 mg).

The first RCT of verapamil was published by Bussone et al in 1990.[[11](javascript:void(0);)] Thirty cCH patients participated in a double-blinded, double-dummy, crossover trial that compared verapamil 360 mg/day to lithium 900 mg/day. Six cCH patients dropped out during the first washout period. Effect measurements were headache index (undefined) and analgesic consumption in the first week. Both treatments significantly improved the headache index and reduced the analgesic consumption by 58% in the first week. Half of the cCH patients experienced benefit from verapamil compared to only 38% when treated with lithium. There was no difference in the consumption of analgesics between the lithium group and the verapamil group. A positive correlation was found between lithium response and plasma concentration, however, no such correlation was found with verapamil. This study established the foundation of treatment with verapamil, but the trial is difficult to relate to other trial outcomes because the headache index is undefined. The temporal relationship between the last administration of verapamil and blood samples of plasma verapamil was not described but is important since verapamil has a half-life of 4–12.5 hours.[[12](javascript:void(0);),[13](javascript:void(0);)] Lithium, however, has a longer half-life of 18–36 hours.[[14](javascript:void(0);)] Therefore, based on these results, we cannot reliably exclude an association between plasma concentration of verapamil and treatment response.

A placebo-controlled study of verapamil in eCH was performed in 2000. Leone et al[[15](javascript:void(0);)] included 30 eCH patients who were randomized 1:1 into a treatment arm (verapamil 120 mg × 3) or a placebo arm (unspecified tablet × 3) with the primary endpoint frequency reduction. At assessment in the second week, the eCH patients suffered from 0.6 CH attacks per day in the treatment arm compared to 1.65 attacks per day in the placebo arm (P < .001). In addition, the use of analgesics was significantly higher in the placebo arm with a mean consumption of 1.2 doses per day compared to 0.5 per day in the treatment arm. Four of 15 CH patients in the treatment arm became pain free and 80% were responders defined as a ≥50% frequency reduction, whereas no responders were reported in the placebo group.

Blau and Engel attempted to personalize treatment based on attack rhythmicity and results from their open-label study of 52 eCH and 18 cCH patients were highly positive.[[16](javascript:void(0);)] The study aimed to prevent CH attacks based on timing the peak verapamil (immediate release) plasma concentration with the expected occurrence of attacks. The authors defined success as complete termination of attacks. In the episodic group, 94% responded with complete termination on 200–960 mg/day of verapamil and 2 needed additional preventive therapy. The therapy regimen was not as effective in the chronic group, where only 10 of 18 patients (56%) had complete cessation of attacks and 8 patients needed additional therapy. Only 1 of 5 included cCH women achieved full suppression of attacks compared with 9 of 13 cCH men. Complete suppression of attacks was achieved by the end of the second week for 47 of 59 patients, who responded defined as attack freedom. However, it is unclear how long it took the remaining patients to achieve complete suppression of attacks. The authors noted that "long-acting" verapamil was less effective than immediate release in a few patients but did not specify how this was investigated.

The acute effect of intravenously administered verapamil was tested in 15 cCH patients with nitroglycerin-induced CH-like attacks.[[17](javascript:void(0);)] In 12 of 15 cCH patients, nitroglycerin (0.9-1.2 mg) induced CH-like attacks (normal site of CH). When the pain peaked (59 ± 17 minutes. after infusion start), each patient received and intravenous injection of Verapamil 5–7 mg (sic). After 16 ± 5 minutes 10 out of 12 patients reported that the pain intensity was more than halved and after 35 ± 16 minutes freedom of pain was achieved in 7 patients. Four patients received placebo at the time of peak pain and there was no reduction of pain within the first 30 minutes, hereafter they received verapamil intravenously. Two responded incompletely to the subsequently administered verapamil and the other 2 had no effect. It is unclear whether the study was randomized or blinded and whether the patients were crossed over from the original study, which would lead to potential bias. The authors did not perform statistical analyses on the efficacy responder rate.

**Other Calcium Channel Blockers.**Verapamil was not the first CCB studied in CH patients. Nimodipine and nifedipine are, as verapamil, voltage-gated CCBs, but they belong to another distinct chemical class, namely the dihydropyridines.[[18](javascript:void(0);)] In the study by Meyer and Hardenberg,[[5](javascript:void(0);)] that proposed verapamil for the treatment of CH, a crossover trial with 2 dosages of nimodipine and an open-label trial of nifedipine was included. Eight cCH patients participated in the crossover trial comparing nimodipine 60 mg vs 120 mg daily. After completed crossover (total duration 4 months) all 8 patients had benefited from nimodipine therapy, and the mean frequency was significantly reduced from 24 attacks/month to 13 attacks/month (P < .006). After 2 months therapy, 5 patients (62.5%) benefited from 60 mg/day and 7 patients (87.5%) benefited from 120 mg/day (no P value was calculated). The same patients participated in the open-label investigation of nifedipine. Nifedipine (mean dose: 60 mg/day, range: 30–180 mg/day) reduced the mean monthly attack frequency from 38 at baseline to 0 at study end, but the treatment period was unknown.

Nimodipine was further investigated in an open-label study by de Carolis et al in 1988.[[19](javascript:void(0);)] Nimodipine was compared to prednisone, lithium, and methysergide. Fifty eCH patients participated of which 13 received nimodipine. The authors defined success as disappearance of attacks within 7 days of treatment and 7 eCH patients fulfilled this criterion. Nimodipine and prednisone both resulted in a >50% response rate, but only 41% responded to lithium and 27% responded to methysergide. Unfortunately, dosages were not specified. Flunarizine (Sibilium®) is used as a migraine preventive,[[20](javascript:void(0);)] but the effect has not been investigated in CH. Only 1 case is described in which the patient suffered from concomitant epilepsy,[[21](javascript:void(0);)] however, complete termination of attacks was achieved with flunarizine treatment.

### Risk of Bias

Five studies support verapamil treatment in CH ([Table 1](javascript:showModal('T1');p)), 2 of which are RCTs (only 1 placebo-controlled) and 3 are uncontrolled open-label studies. Outcome assessment is not described as blinded in the 3 open-label studies and the risk of bias is high in such studies.[[22](javascript:void(0);)] Both RCTs are double-blinded and randomized, however, none of the publications describe this process in detail. Protocols are, given the age of the studies, not available at [clinicaltrials.gov](http://clinicaltrials.gov). It appears that there are no missing data, but the authors do not specifically comment on this issue in the publications. The studies are graded as AAN Classes II and III,[[23](javascript:void(0);),[24](javascript:void(0);)] resulting in evidence level C. The RCT studies applied the correct methodology, however, the details are not described, and therefore, the risk of bias of the results is unclear. All 5 studies present positive results, thus publication bias cannot be ruled out and other bias can be present in the 3 open studies.

Nimodipine was studied in 1 RCT and 1 open-label study. In the RCT, the risk of selection bias is unclear, however, the performance bias and patient-reported outcomes are judged to be in low risk of bias. Nifedepine was only studied in an open-label design. The patients were not randomized to the different treatments and no blinding was described increasing the risk of bias.

### Side Effects and Safety

Even though verapamil is safe and relatively well-tolerated[[15](javascript:void(0);)] side effects do occur. In the 5 cited studies, side effects were observed in 12–86% of patients, and most were deemed mild.[[5](javascript:void(0);),[10](javascript:void(0);),[11](javascript:void(0);),[15](javascript:void(0);),[16](javascript:void(0);)] The negative inotrope and chronotrope effects of verapamil[[25](javascript:void(0);)] are a concern for the neurologist when treating CH patients with "neurological dosages" of verapamil, which are roughly twice those used in cardiac diseases.[[6](javascript:void(0);)] Verapamil has been shown to induce cardiac side effects in otherwise healthy patients with no history of cardiac disease[[26](javascript:void(0);)] and can induce a slight reduction in blood pressure in normotensive patients.[[27](javascript:void(0);)] In a review, including 217 CH patients treated with verapamil (mean dose 512 mg/day [range 20–1200 mg/day]),[[28](javascript:void(0);)] electrocardiography (ECG) descriptions were provided for 108 (mean dose 587 mg/day [range 240–1200 mg]). Of these 21 CH patients had atrioventricular conduction abnormalities (19%) (mean dose 567 mg/day [range 240–960 mg/day]) and 39 had bradycardia (HR < 60 bpm) (36%). A high dosage of verapamil is sometimes needed to achieve effect in CH and 1 study found that 29 of 200 CH patients (15%) were treated with dosages of verapamil ≥720 mg[[29](javascript:void(0);)] which resulted in ECG abnormalities in 11 patients (38%). Of these, 4 were classified as serious adverse events including AV block (2 first degree, 1 second degree, and 1 third degree).[[29](javascript:void(0);)] In 3 of 4, the serious adverse events had delayed onset where the event occurred years after the high dosage was achieved.

In an international Delphi study 40 cardiologists, who specialized in cardiac arrhythmias, had divergent opinions on how to monitor verapamil treatment.[[30](javascript:void(0);)] The only consensus recommendation made was to secure a baseline ECG before initiation of treatment. However, most cardiologists recommended repeating the ECG 5 days after each increase in verapamil dosage. Furthermore, a pretreatment ECG was not deemed necessary in patients who had not suffered from cardiac side effects during a previous bout treated with verapamil. Half of the specialists recommended a Holter ECG when dosages exceeded 480 mg/day.[[30](javascript:void(0);)] American Headache Society and European Federation of Neurological Societies recommend ECG monitoring.[[23](javascript:void(0);),[31](javascript:void(0);)]

Other side effects to verapamil include constipation, ankle edema, stomach cramps, nausea, dizziness, sleep disruption, and rash.[[32](javascript:void(0);)] Identified serious side effects, beside cardiac effects, are lymphomatoid rash (dose: 240 mg/day)[[33](javascript:void(0);)] and gingival hyperplasia (dose: 400–760 mg/day).[[34](javascript:void(0);)] Furthermore,1 case of Stevens-Johnson syndrome 2 days after first dose of 200 mg verapamil has been published.[[16](javascript:void(0);)] Verapamil used to treat hypertension is not found to have increased risk of gingival hyperplasia compared to controls.[[35](javascript:void(0);)]

**Basic Pharmacology of Verapamil.—**Verapamil is a CCB that affects voltage-gated calcium channels by binding to the alpha1-subunit of the voltage-gated calcium channel complex.[[36](javascript:void(0);)] Normally, the channels open in response to a depolarization,[[36](javascript:void(0);)] which allows an influx of calcium. The influx of calcium initiates several different events[[37](javascript:void(0);)] including synaptic transmission,[[38](javascript:void(0);)] enzyme activity and gene expression.[[39](javascript:void(0);)] The binding properties of verapamil are diverse and verapamil is found to bind to the Cav1.2,[[40](javascript:void(0);)] Cav1.3,[[41](javascript:void(0);)] Cav3.3,[[42](javascript:void(0);)] Cav3.1,[[43](javascript:void(0);)] Cav2.2,[[44](javascript:void(0);)] and Cav2.[[144](javascript:void(0);)] transmembrane subunits. Cav1.2 is the subunit in L-type calcium channels (for complete list of nomenclature see [Table 2](javascript:showModal('T2');p)). Verapamil can also inhibit potassium channels[[45](javascript:void(0);),[46](javascript:void(0);)] and interacts with a sodium channel.[[47](javascript:void(0);)]

**Pharmacokinetics of Verapamil.[**[**13**](javascript:void(0);)**,**[**48–50**](javascript:void(0);)**]—**Verapamil is almost completely absorbed from the gut (80–90%),[[51](javascript:void(0);)] but undergoes extensive first pass metabolism mediated by cytochrome p450[[52](javascript:void(0);)] in the liver and the resultant bioavailability of verapamil is 20–35%.[[12](javascript:void(0);),[13](javascript:void(0);)] Verapamil is metabolized by CYP3A, which is found to have a minor diurnal pattern,[[53](javascript:void(0);)] with CYP3A activity lowest around 3 AM and highest in the afternoon. The plasma concentration of verapamil after administration of immediate release verapamil varies greatly and is more stable after administration of sustained release tablets[[49](javascript:void(0);)] ([Table 3](javascript:showModal('T3');p)). Plasma concentration and bioavailability of verapamil depend on multiple factors. The bioavailability of sustained release tablets is around 90% compared to immediate release but with a large variability.[[49](javascript:void(0);),[54](javascript:void(0);)] With immediate release tablets the bioavailability is increased by 5%-points in women compared to men.[[55](javascript:void(0);)] Normally, immediate release verapamil peaks in plasma concentration after 1–2 hours,[[49](javascript:void(0);)] but the level is dependent on time of dosage. The highest plasma concentration is achieved in the morning compared to the afternoon, evening, or nighttime (immediate release),[[56](javascript:void(0);)] however, this is a single-dose study and might not be relevant in steady state. Bioavailability is not affected by food intake other than extensive intake of grapefruit.[[48](javascript:void(0);),[57](javascript:void(0);)] The plasma concentration of verapamil is less fluctuating with the sustained release formulation and peak concentration appears after 5–9 hours.[[48](javascript:void(0);),[49](javascript:void(0);)] There is no difference in time of dosage regarding peak concentration for sustained release, but the half-time is slightly elevated during morning administration.[[58](javascript:void(0);)] The clearance of orally administered sustained release verapamil is found to be higher in women compared to men, afro-americans compared to caucasian and smokers compared to non-smokers.[[54](javascript:void(0);)] Smoking causes a 25% of reduction in verapamil concentration compared to non-smokers.[[59](javascript:void(0);)]

The multiple interactions of verapamil are complex.[[60](javascript:void(0);)] Treatment with verapamil elevated the serum concentration of ethanol, possibly due to inhibited elimination.[[61](javascript:void(0);)] Verapamil interacts with many drugs,[[62](javascript:void(0);)] however, regarding CH treatments there is a synergistic/additive interaction between verapamil and lithium and combined treatment might result in side effects from multiple organs.[[63](javascript:void(0);)] In a case report, neurotoxic side effects (vomiting, muscular weakness, and ataxia) occurred even when lithium was in the therapeutic interval.[[64](javascript:void(0);)] Thus, the combination requires caution and follow-up. No interactions are currently described regarding oxygen, sumatriptan, candesartan, melatonin, gabapentin, topiramate, or sodium valproate. Thus, according to literature, it appears that grapefruit juice drinking, non-smoking men would achieve the highest concentration.

Verapamil is lipophilic and easily crosses the blood–brain barrier. However, the verapamil concentration in the central nervous system (CNS) is very low due to P-glycoprotein (Pgp), which continuously transports verapamil out of the brain.[[65](javascript:void(0);),[66](javascript:void(0);)] In transporter knockout mice that completely lack Pgp, the brain–blood ratio (R)-[11C]verapamil was 7.9 ± 0.5 compared to wild-type mice where the ratio was 1.3 (±0.1) (P < .0001). A possible mechanism to enhance the neurological effect of verapamil, and limit the cardiac side effects, could therefore be to inhibit Pgp. However, the Pgp inhibitor telmisartan (angiotensin-II-receptor antagonist approved for hypertension) is likely not promising.[[67](javascript:void(0);)] Infusion with tariquidar (a third generation Pgp inhibitor) has been shown to induce near complete inhibition of Pgp and increases the total distribution volume of (R)-[11C]verapamil in the CNS by 273 ± 78%.[[68](javascript:void(0);)] However, other third generation Pgp inhibitors have been successful in preclinical investigations, but have not enhanced the clinical effectiveness of antidepressant drugs[[69](javascript:void(0);)] and even if there is a great therapeutic gain, the practicalities of infusion medication are difficult to implement in clinical practice. Given that Pgp inhibition weakens the blood–brain barrier, the risk of central adverse events may be increased.

**Pharmacodynamics of Verapamil.—**The cardiovascular pharmacodynamics of verapamil are well described but the neurological less so.[[6](javascript:void(0);),[36](javascript:void(0);)] The complexity is high, since the same neuron has multiple types of channels, each with more accessory subunits, and neuronal firing patterns are heterogenic.[[36](javascript:void(0);)] L-type calcium channels are widely expressed in the CNS, and mainly located in dendrite spine and shafts. A single neuron will typically express different receptor subfamilies.[[70](javascript:void(0);)] CCBs are currently used in the treatment of neurological and psychiatric disorders such as epilepsy,[[71](javascript:void(0);)] Parkinson's disease,[[72](javascript:void(0);)] dementia,[[73](javascript:void(0);)] bipolar disorder,[[74](javascript:void(0);),[75](javascript:void(0);)] and long-term depression.[[18](javascript:void(0);)] Dementia and Parkinson's diseases are neurodegenerative disorders, whereas CH, epilepsy, depression, and bipolar disorders have a cyclic nature with a possible, common hypothalamic link.[[76](javascript:void(0);)] The following section focuses on mechanisms of calcium channels in the brain important in CH.

The hypothalamus is suspected to play a central role in CH pathophysiology[[1](javascript:void(0);)] and CH has pronounced chronobiological features.[[77](javascript:void(0);)] Calcium homeostasis is closely associated with circadian rhythms[[78](javascript:void(0);),[79](javascript:void(0);)] and has been suggested to be a clock-controlled messenger, and not a generator of rhythmicity.[[80](javascript:void(0);)] Current through the voltage-gated calcium channels and intracellular calcium are reduced during the night, and nimodipine reduces the day-time current more than the night-time current.[[81](javascript:void(0);)] In cell cultures from mice, the amplitude of the circadian rhythm is reduced during pharmacological inhibition of calcium channels (using verapamil and diltiazem).[[74](javascript:void(0);)] Examination of rBmal1 mRNA, which has a crucial function in circadian oscillation, reveals that an inhibition of fluctuations occurs during a non-selective pharmacological inhibition of calcium channels.[[82](javascript:void(0);)]

The L-type calcium channel Cav1.2 is considered important in resetting the circadian rhythm during late night.[[83](javascript:void(0);)] Regarding sleep it has been shown, that a specific CACNA1C gene is associated with sleep quality[[84](javascript:void(0);)] and may be associated with sleep latency,[[85](javascript:void(0);)] which is prolonged in CH patients.[[86–88](javascript:void(0);)] Thus, L-type calcium channel antagonists may normalize sleep.[[75](javascript:void(0);)] A recent study from our own group found that CH patients taking verapamil had a later nocturnal attack peak compared to CH patients not taking verapamil (02:43 AM compared to 01:53 AM).[[77](javascript:void(0);)] This might suggest that verapamil delays the attacks, however, other explanations are also possible.

Calcitonin gene-related peptide (CGRP) is elevated during CH attacks[[89](javascript:void(0);)] and can provoke CH attacks.[[90](javascript:void(0);)] CGRP is believed to play a role in central sensitization[[91](javascript:void(0);)] and CGRP-release is controlled by voltage-gated calcium channels.[[92](javascript:void(0);)] In the literature, the relation between verapamil and CGRP has not been studied, however, other CCBs decreased CGRP-release. In rats, blockade of P/Q-, N-, and L-type voltage-gated calcium channels significantly decreased the potassium-induced CGRP-release.[[93](javascript:void(0);)] In another rat study, nimodipine administered in relevant dosages intraperitoneally over a fortnight significantly downregulated CGRP in the trigeminal nucleus caudalis. In contrast, morphine resulted in an upregulation of CGRP[[94](javascript:void(0);)] and verapamil does not seem to act through the opioid system.[[95](javascript:void(0);)] These studies might suggest that blockage of calcium release inhibits the CGRP-mediated hyperresponsive state, however, we need more basic science research to draw firm conclusions.

### Conclusion and Future Directions

Studies of a cyclic disorder such as CH are notoriously hard to design and even harder to execute but the severity and burden of CH call for directed efforts to provide effective preventive treatment. Overall, the evidence supporting the effect of available preventive treatments in CH is sparse and the above-mentioned studies on the effect of verapamil have methodological limitations. However, available trials, clinical experience, and the test of time have proven that verapamil, in particular, is an effective treatment.

At present, verapamil treatment is initiated off-label by the physician with the risk of side effects and an unknown effect in the individual patient. Based on the 5 presented studies, we expect that 50–94% of the patients are responders. However, we do not have certain predictors of response, ie, cCH/eCH-phenotype, or sex. Even though the studies were not designed to identify responder rates in subgroups, there is some data, which can be extracted. Thus, cCH is harder to treat with verapamil than eCH, however, a direct comparison of the 2 relevant RCTs was not possible. The chronotherapeutic approach might increase the response to verapamil, but the cCH patients still do not seem to respond as quickly or as efficiently as the eCH patients do, which may complicate the treatment regime. The gender difference has not been investigated systematically, but it appears that women have less effect of verapamil. Since male and female CH patients do not differ in phenotype,[[96](javascript:void(0);)] a possible difference in treatment response might in some part be caused by differences in pharmacokinetics, which should be investigated further. Physicians might consider initiating non-smoking men with a lower starting dose or extended up-titration. To develop personalized treatment with verapamil the suspected relationships between plasma concentration and effect should be confirmed and further research is needed regarding enzyme activity, pharmacokinetics, and efficacy, ideally collected prospectively.

If the effect of verapamil depends on the concentration, the current 3 different release forms of verapamil offer some opportunity to personalize treatment. For example, an extended onset release capsule could be an option if the patient suffers from early morning attacks and immediate release as an evening dose for patients who suffer from attacks in the early night. Intravenously administered verapamil indicate that the effect may not only be preventive, but also acute, and it could be an option for severely affected patients as an inpatient treatment alongside dihydroergotamine infusion.[[97](javascript:void(0);),[98](javascript:void(0);)] Significant ECG changes can develop, even on a stable dosage[[28](javascript:void(0);),[29](javascript:void(0);)] in patients with no prior history of cardiac disease. Dihydropyridines (eg, nimodipine) lack direct negative cardiac effects and therefore the side effect profile might be more attractive. Why nimodipine and nifedipine were not investigated further after the excellent open label results remains an unknown. Dihydropyridines are also used to treat other cyclic hypothalamic conditions such as bipolar disorder. Especially nimodipine is of interest due to the high brain–plasma ratio.[[99](javascript:void(0);)] Therefore, we might consider resurrecting other CCBs in the treatment of CH, however, the effect should be investigated properly in a randomized placebo-controlled trial.

**Potential Mechanisms of Verapamil in Cluster Headache.—**The hypothalamus and trigeminal autonomic reflex play a major part in CH pathophysiology, but the integrated disease mechanism remains unresolved. Thus, understanding verapamil's effect mechanism might increase our understanding of the disease itself. Based on the available studies, we hypothesize that verapamil modulates circadian oscillations or CGRP-release through its ability to block calcium channels. The specific effects of blocking calcium channels in the CNS requires focused basic science efforts before conclusions can be drawn. With this review, we hope to inspire future pharmacological studies of verapamil and development of a more individualized and specific CH prevention.