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# Valproate semisodium ER for migraine and cluster headache prophylaxis.

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Importance of the field: Migraine and cluster headache are disabling syndromes that often require prophylactic treatment. Valproate semisodium ER is FDA-approved for the treatment of epilepsy, acute mania in bipolar disorder, and migraine prophylaxis.

Areas covered in this review: We reviewed literature regarding valproate semisodium ER pharmacokinetics and its use in migraine and cluster headache prophylaxis.

What the reader will gain: Valproate semisodium ER is well-studied and effective in the preventive treatment of migraine and cluster headache. This article reviews the evidence for its use, describes how to administer and dose this medication, and reviews important safety precautions.

Take-home message: Valproate semisodium ER is effective in the prophylactic treatment of migraine and cluster headache. This once-a-day dosing formulation may increase compliance.

Keywords: Cluster headache, migraine prophylaxis, valproate, valproate semisodium ER

## **1. Introduction**

### **1.1 Migraine headache**

Migraine is a common neurologic disorder characterized by multiple usually severe attacks of head pain and associated symptoms. A typical migraine attack lasts from four to 72 hours.

Migraine pain characteristics include pulsating quality, moderate to severe pain, unilateral location, and aggravation by or avoidance of physical activity [1]. Associated symptoms that accompany headache include photophobia (light sensitivity; 81.9%); phonophobia (sound sensitivity; 77.9%), and nausea (60%) [2]. Some migraineurs experience reversible neurologic symptoms called aura. Migraine auras usually last between five and 60 minutes and may include visual, sensory, or motor symptoms. Patients may experience fully reversible visual symptoms, such as flickering lights, spots or lines, or even loss of vision. Some have pins and needles sensations, numbness, or fully reversible speech disturbance [3]. Prior to the migraine attack, some individuals experience a prodrome, which occurs hours to days before the headache begins. Some of the prodrome symptoms are irritability, depression, fatigue, neck stiffness, diarrhea, constipation, and food cravings [4].

Four to seven percent of men and 15 to 20 percent of women suffer from migraine, with the highest migraine prevalence experienced by women between the ages of 25 and 55 [2]. When

migraine attacks are severe, patients usually require acute medication for treatment. Non-steroidal anti-inflammatory drugs (NSAIDs), triptans, and dihydroergotamine (DHE) are among the acute medications commonly used to treat migraine. Migraine prophylaxis, including medications such as valproate semisodium ER (VPS ER), is recommended for patients with frequent or particularly disabling attacks [5]. Migraine pathophysiology is becoming better understood, and some important concepts include cortical spreading depression, the release of inflammatory neuropeptides such as calcitonin gene related peptide (CGRP) and substance P, brain hyperexcitability, and central sensitization of the trigeminal nucleus caudalis [6-9].

## **1.2 Cluster headache**

Cluster headache (CH), which can be more disabling than migraine, can also be treated with VPS ER. CH prevalence is somewhere between 56 and 401 per 100,000 and, unlike migraine, is more common in men [10]. CH attacks are usually located in or around one eye, with at least one ipsilateral autonomic feature, such as conjunctival injection, nasal congestion, rhinorrhea, facial sweating, and eyelid edema, with miosis or ptosis present. The pain may be described as sharp, knife-like, or stabbing. The attacks of excruciating unilateral head pain are intermittent and short-lived, lasting from 15 to 180 minutes. Unlike migraine patients, patients with CH generally do not lie still during attacks and may pace with agitation and restlessness [11, 12]. Acute CH medications include triptans, dihydroergotamine (DHE), inhaled oxygen, and intranasal lidocaine or capsaicin [12-15]. Often CH occurs in cycles lasting weeks to months at a time with prolonged remissions. Because CH is occasionally refractory to acute pain medication, or patients may have many attacks that require acute treatment, cluster patients usually require preventive medication when in cycle to reduce attacks and disability. Common preventive medications include verapamil, methysergide, corticosteroids, topiramate, lithium, and forms of valproic acid, such as VPS ER. Corticosteroids may be indicated as a faster acting preventive treatment at the start of a cycle [16-18].

## **2. Overview of preventive therapy**

### **2.1 Reason for preventive therapy**

Although migraine is an episodic disorder, many patients suffer frequent, disabling attacks. Preventive therapy, such as VPS ER, may help reduce the frequency, duration, or severity of attacks [5] and appears to reduce the risk for developing chronic migraine or medication overuse headache [20]. Preventive therapy should be implemented when one of the following headache conditions exists: 1) A diagnosis of hemiplegic migraine or migraine that could lead to permanent neurologic injury. 2) Migraines that occur more often than once a week, as this may lead to the development of chronic migraine or acute medication overuse. 3) Acute medication overuse. 4) Patient's wish to be placed on prophylactic medication. 5) Acute medication causes adverse events (AEs) or is not effective. 6) Patient's life is severely impacted even though he or she is using acute medications. Based on these criteria, population-based surveys suggest that migraine prophylaxis is underutilized; migraine prophylaxis is indicated for 1 of 3 patients but only 3 to 13% use them [21-22].

### **2.2 Overview of the market for migraine preventive treatment**

Most migraine preventive medications are used off-label, since the medications have usually been developed for other indications, such as depression, epilepsy, or hypertension. These preventive medications include antiepileptic drugs (AEDs), antidepressants, antihypertensives, and botulinum toxin. Many were serendipitously proven to be helpful for migraine prophylaxis. A brief overview will be provided in this section; not all medications will be listed and no dosages will be given, as this is meant to be a quick synopsis of other preventive medications used. AEDs used to treat migraine include carbamazepine, gabapentin, lamotrigine, topiramate, and VPS ER. Commonly used antidepressants include tricyclic compounds (amitriptyline, nortriptyline, protriptyline) and serotonin-norepinephrine reuptake inhibitors (venlafaxine,

duloxetine). Commonly used antihypertensives include many beta blockers (atenolol, metoprolol, nadolol, propranolol, timolol), calcium channel blockers (verapamil), and angiotensin-converting enzyme inhibitors (lisinopril) [5]. Some natural products, such as riboflavin, butterbur, and coenzyme Q10, appear effective for migraine prophylaxis. Due to its safety, magnesium is one option for pregnant women who require migraine prophylaxis [23-26]. Nevertheless, some preventive medications have been shown to be more efficacious than others in randomized, controlled trials. Topiramate, VPS ER, amitriptyline, metoprolol, propranolol, timolol, and butterbur are among those with Class I trial proven efficacy. VPS ER, topiramate, propranolol, and timolol are the only available FDA-approved medications in the United States for the preventive treatment of migraine [27]. Methysergide, an ergot and agonist and antagonist of different serotonin receptors, is effective in migraine prophylaxis but has multiple reported AEs, including fibrotic disorders, and is no longer available in the United States.

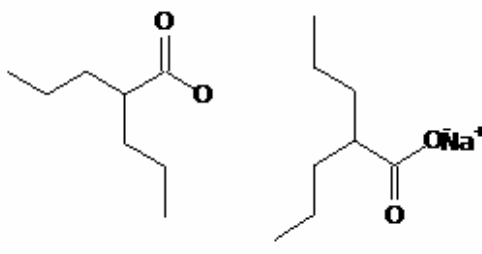
### 3. Clinical Pharmacology

#### 3.1 Description

VPS ER is comprised of sodium valproate and valproic acid in a 1:1 relationship. The chemical name is sodium hydrogen bis (2-propylpentanoate). VPS ER dissociates into valproate ion within the gastrointestinal tract. It comes in strengths of 125 mg, 250 mg, and 500 mg [28]. VPS ER is the international nonproprietary name. Other formulations of VPS ER appear to work in the same manner and are generally grouped together as the same medication. The other names of this medication will be referred to in this article as there simply are not enough studies on VPS ER alone. Other terms include valproate, valproic acid, divalproex sodium, sodium valproate. [29]

#### Drug Summary Box

Drug name	Valproate semisodium, ER
Phase	Launched
Indications	Migraine prophylaxis

Pharmacology description	Sodium channel antagonist GABA receptor agonist Voltage-gated sodium channel inhibitor
Route of administration	Alimentary, po
Chemical structure	
Pivotal trial(s)	Table 1, Table 2

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### 3.2 Pharmacodynamics/mechanism

The exact mechanism of action for the therapeutic effect of VPS ER is unclear, but there are many possible causes. It inhibits gamma-aminobutyric acid (GABA) transaminase and the catabolism of GABA, an inhibitory neurotransmitter. It is also postulated that increased GABA concentrations are present from activation of glutamic acid decarboxylase. VPS ER is also a sodium channel antagonist, modulates calcium channels, and may suppress N-methyl-D-aspartic acid (NMDA) excitatory neurotransmission. It is also postulated that VPS ER stops the 5-HT neurons of the dorsal raphe from firing and modulates serotonergic and dopaminergic transmission. Preventive medications such as VPS ER have many different mechanisms of action, including actions at serotonin and norepinephrine receptors, modulation of sodium and glutamate, and inhibition of nitric oxide production. [29-30] VPS ER may suppress cortical spreading depression (CSD), a depolarization or excitation of neuronal and glial membranes that move across the cortex at a rate of three to five millimeters per minute, which is then followed by a wave of inhibition [31]. Suppression of CSD could be an important mechanism of action for all effective migraine prophylactic medications. [32]. These mechanisms suggest that VPS ER, like

many other migraine preventive drugs, is effective over time due to reduction of cortical hyperexcitability.

### **3.3 Pharmacokinetics**

Average bioavailability of VPS ER given once-daily under both non-fasting and fasting conditions was 89% relative to an equal total dose of VPS given two, three, or four times a day.. VPS ER is a weak inhibitor of multiple CYP-P450 isozymes. VPS ER is bioequivalent to VPS when VPS ER is given in an eight to 20 percent higher dose than VPS [33-34].

### **3.4 Metabolism/excretion**

VPS ER undergoes hepatic metabolism via the CYP-P450 system. Mitochondrial beta oxidation accounts for over 40% of its metabolism and is the other major metabolic pathway. The mean terminal half-life for VPS ER monotherapy ranges from 9 to 16 hours following oral doses of 250 to 1000 mg. Patients on enzyme-inducing antiepileptic drugs, such as phenytoin, carbamazepine and phenobarbital, will clear VPS ER more rapidly, with a half-life of 5-12 hours. Elderly patients and those with hepatic dysfunction eliminate VPS ER more slowly. The half-life increases to 12 to 18 hours in individuals with significant liver impairment [29].

### **3.5 Overall safety and tolerability**

VPS ER use is associated with multiple potential AEs. VPS ER has a similar or somewhat lower AE rate compared with other forms of valproate, such as immediate-release forms. In one study, the two forms divalproex and divalproex ER had similar AEs [34], but in another divalproex study, the extended-release version avoided high peak serum drug levels and is thus postulated to have fewer AE's. The study concluded that individuals on the extended-release form had fewer tremors and gastrointestinal complaints and less weight gain [35-36]. The once-daily dosing of VPS ER may increase medication compliance and decrease rates of discontinuation [37].



In placebo-controlled migraine trials, divalproex sodium users were shown to have more AEs compared to patients who were given placebo. Gastrointestinal (GI) symptoms were the most commonly reported AEs in migraineurs. GI AEs include nausea (31%), dyspepsia (13%), diarrhea (12%), vomiting (11%), and abdominal pain (9%). Asthenia (20%), somnolence (17%), dizziness (12%), tremor (9%), weight gain (8%), back pain (8%), hair loss (7%), and increased appetite (6%) also were noted [38]. Decreasing the dose or adding propranolol (a beta-blocker commonly used to treat essential tremor and migraine) can reduce tremor [39].

Other common AEs noted in the treatment of epilepsy and mania include diplopia, blurred vision, and cognitive problems. Peripheral edema, bronchitis, pharyngitis, and carnitine depletion may also occur [40]. Gastrointestinal symptoms usually decrease after six months and may be alleviated if VPS ER is taken with food. In rare cases, pancreatitis can occur months to years after initiating VPS ER, but it is usually not fatal. Sudden nausea, vomiting, and anorexia may indicate hepatotoxicity and requires caution [41]. VPS ER may be a risk factor for the development of polycystic ovarian syndrome (obesity, elevated androgen concentrations, anovulation, and hirsutism) [42].

More serious AEs include hepatic toxicity, which may cause nausea, anorexia, or jaundice. Hyperammonemia can cause delirium or tremor and may occur even with normal hepatic function testing. VPS ER may cause liver enzyme elevation or thrombocytopenia. Most liver enzyme elevations are mild and transient. If hepatic transaminase levels are mildly elevated, VPS ER can be continued at the same dose or at a slightly lower dose until the values normalize. Patients with elevated ammonia levels may have no clinical symptoms and routinely checking ammonia levels in patients without clinical symptoms is not recommended. Encephalopathy is a rare but severe AE that may occur with or without hepatic dysfunction [43]. Patients should have liver function testing and platelet counts obtained prior to starting the medication. During initial VPS ER use, patients may be monitored every couple of months, and then twice a year to ensure safety. Monitoring valproate levels may be considered. This can be helpful if a patient is not

achieving optimal results, as the valproate level could actually be low and VPS ER can be increased until the level reaches a therapeutic range. The accepted therapeutic range in epilepsy is between 50 and 100 mcg/ml. The therapeutic range for preventing migraine or CH is unknown. The recommended time at which valproate levels should be obtained is 24 hours after dosing, as this will be the drug trough concentration [30].

### **3.6 Precautions**

VPS ER is contraindicated for patients with preexisting thrombocytopenia, liver disease, urea cycle disorders, or pancreatitis. Hepatotoxicity usually occurs within the first six months of use and children under the age of two are at highest risk of developing hepatotoxicity; migraine and CH patients are at a relatively low risk. Facial edema, anorexia, and vomiting may occur.

Hepatotoxicity secondary to treatment with VPS ER may respond to carnitine, a co-factor in the mitochondrial beta-oxidation of fatty acids [44]. Pancreatitis is rare but can occur at the start of treatment. Typical symptoms include nausea, vomiting, abdominal pain, and anorexia.

Hyperammonemia may occur with VPS ER, and liver function tests are insensitive as a marker for hyperammonemia. If a patient develops lethargy, vomiting, and changes in mental status; order an ammonia level. Patients receiving concomitant VPS ER and topiramate therapy need to be closely monitored, as this may increase the risk of developing high ammonia levels [45].

Suicidal thoughts or behavior have also been reported in patients taking AEDs [46] resulting in an FDA warning for all of these drugs. The actual risk of AEDs provoking suicide is under debate [47].

### **3.7 Teratogenicity**

VPS ER is considered a risk category D medication for use in pregnancy [48] and its use by pregnant patients with migraine or bipolar disorder is highly discouraged. The offspring of women who take VPS ER during pregnancy, especially in the first trimester, have an increased

risk of neural tube defects. Babies born to mothers who take VPS ER during pregnancy have a one to two percent chance of developing spina bifida. Other congenital anomalies include craniofacial defects and cardiovascular malformations. Pregnant women on VPS ER should be considered high risk and these women should take folate. Folic acid is recommended to treat women on AEDs at preconception and during the first two to three months of pregnancy to help protect against neural tube defects. Four to five mg of folic acid per day is recommended prior to a planned pregnancy. Folic acid is protective against neural tube defects, but not other anomalies [49]. The risk of developing congenital malformations appears higher with valproate as compared to newer AEDs. A systematic literature review evaluated pregnant women with epilepsy and the effect of AEDs on the fetus. Fetuses born to women taking valproate were the most likely to have malformations (10.73% of births), such as craniofacial, or digital abnormalities, cardiac disorders, and limb defects, when compared to other AEDs including phenytoin (7.36%), phenobarbital (4.91%), carbamazepine (4.62%), and lamotrigine (2.91%) [50]. Valproate may also have a negative effect on later language and behavioral development [51]. VPS ER is secreted in breast milk, but at a lower concentration than most other antiepileptic medications [52]. Women with migraine generally should avoid VPS ER when they are nursing.

### **3.8 Drug interactions/contraindications**

VPS ER is a weak inhibitor of the hepatic CYP450 system and causes interactions by displacing other medications from plasma proteins and inhibiting hepatic metabolism. VPS ER increases plasma levels of many AEDs, such as carbamazepine, lamotrigine, phenobarbital and ethosuximide [53]. VPS ER may increase free levels of phenytoin, which can cause toxicity even if total serum levels are in the normal therapeutic range. It can also increase levels of warfarin, amitriptyline, nortriptyline, zidovudine, valium, cimetidine, chlorpromazine, erythromycin, and

nimodipine, among other medications. An individual who received a 50 mg dosage of amitriptyline/nortriptyline while taking valproate 500 mg bid had a twenty-one percent decrease in plasma clearance of amitriptyline and a thirty-four percent decreased clearance of nortriptyline. Amitriptyline levels must be monitored to make sure that they are not high. The tricyclic antidepressant dosage should be lowered when using valproate in combination with tricyclic antidepressants. Valproate increases the risk of serious rash, such as Stevens Johnson's syndrome, when used concurrently with lamotrigine VPS ER may increase the effects of CNS depressants, such as barbiturates and benzodiazepines. Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. The free fraction of diazepam is increased and diazepam plasma clearance and volume of distribution is reduced as a result [54]. Patients should not operate machinery or drive vehicles until they are aware of how they will react to the medication. Multiple medications affect the metabolism and clearance of VPS ER. Erythromycin, felbamate, and chlorpromazine can increase VPS ER levels and toxicity and salicylates increase the amount of free VPS ER [55]. CYP450 inducers, such as phenytoin, phenobarbital, primidone, cholestyramine, rifampin, and carbamazepine, may lower VPS ER levels—even doubling the clearance of valproate. This means that patients on monotherapy will tend to have longer half-lives and higher concentrations of the drug than patients receiving polytherapy with some antiepileptic drugs. A lower VPS ER level due to the use of enzyme inducers can lead to treatment failure. Hyperammonemia and encephalopathy are more common with the concomitant use of topiramate and VPS ER. [45].

#### **4 Clinical efficacy of VPS ER in headache disorders**

##### **4.1 Efficacy of VPS ER in migraine prophylaxis**

Several studies prove the efficacy of VPS ER and its similar formulations as a prophylactic treatment for migraine. One multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial found VPS ER to be effective in the prophylactic treatment of migraine

headache. Patients were started on a dose of 500 mg once daily for one week, and then the dose was increased to 1000 mg once daily, with an option to scale it back to 500 mg during the second week if the patient experienced AEs. The mean reduction was 1.2 attacks during a four-week period from a baseline mean of 4.4 in the VPS ER group, compared with 0.6 fewer attacks from the baseline mean of 4.2 in the placebo group [56]. In another study, the efficacy of sodium valproate for migraine was evaluated in a double-blind, randomized, crossover study. The individuals were placed on 400 mg of sodium valproate twice per day and 86.2 percent of 29 patients had a reduction in the frequency or severity of attacks. The mean number of attacks was reduced from 15.6 to 8.8. [57]. In another study, 44% of 132 subjects taking divalproex sodium had a 50% or greater reduction in migraine frequency, compared with 21% of the placebo group [58]. A study of slow-release sodium valproate with 43 patients who had migraine without aura using a triple-blind, placebo- and dose-controlled, crossover study revealed 65% of the treatment group had a reduction in migraine frequency, compared with 18% for placebo [59]. Matthew and Silberstein, in a randomized, placebo-controlled study of divalproex sodium, 500-1500 mg/day, demonstrated 48% rate of response (50% or greater reduction in attack frequency) compared with 14% of placebo group [60]. Apostol et al did not, however, find that VPS ER was effective in adolescents with migraine compared with placebo, although 75% reported improvement with few AEs [61-2] [Table 1].

Migraine treatment is usually effective within a couple of weeks, but it may take as long as three months for it to become fully effective. If VPS ER is not helpful with migraines, one might consider ordering a drug level to make sure that the patient has full benefit of the drug and to monitor compliance. Conversely, if a patient has minimal headaches after six months of being treated with VPS ER, one may consider tapering or reducing the dose. It should also be stopped if the patient is considering pregnancy.

#### **4.2 Efficacy of VPS ER in cluster headache prophylaxis**

While prophylaxis of CH is not an FDA-approved indication, VPS ER appears to be effective in the preventive treatment of CH. There are currently no approved FDA-approved medications for CH prophylaxis. The evidence for the use of VPS ER in the prevention of CH is weaker than in migraine. In an initial open clinical trial, 73% reported improvement using doses ranging from 600 mg to 2000 mg/day [63]. Large retrospective studies confirm these results [64]. But a double-blind, placebo-controlled study using sodium valproate 1000-2000 mg/day for CH showed a non-significant difference in the two groups, possibly due to improvement in the placebo group (62% of the placebo group improved) [65] [Table 2]. It has been suggested that CH patients with migrainous features may be good candidates for VPS ER [66]. Intravenous valproic acid may be effective in refractory CH [67].

## **5. Expert opinion**

VPS ER is an effective medication for migraine and CH prophylaxis, as it is one of only a few drugs the FDA has approved for migraine and with multiple studies that demonstrate its effectiveness. It also appears effective for some patients with CH, but without good evidence from placebo-controlled trials. In addition to these two headache conditions, it may also be used with some efficacy in trigeminal neuralgia [68]. VPS ER is also effective for bipolar disorder and epilepsy—common co-morbid conditions in migraine patients. The once-daily VPS ER may have less sedation and be more likely to improve compliance. Serum levels are reliable and can help guide optimal dosing. Unlike phenytoin, a class 1b antiarrhythmic agent, there are no cardiac risks. Unlike many migraine preventives, VPS ER is safe in the setting of affective disorders and does not affect blood pressure or heart rate. Migraine prophylactic treatment can improve quality of life and reduce disability. If patients do not improve with VPS ER, consider ordering a drug level to monitor compliance and make sure that the patient has full benefit of the drug. VPS ER appears to be among the most effective migraine and CH prophylactic treatments. Intravenous valproic acid may even be helpful in the acute treatment of migraine and cluster attacks [69-70].

The use of VPS ER is limited, however, by bothersome and common AEs. These include GI distress, weight gain, tremor, alopecia, polycystic ovary syndrome, and, rarely, life-threatening conditions, such as liver failure or pancreatitis. Unfortunately, these AEs are often unpredictable and due to idiosyncratic reactions. Although some abnormalities (transient liver enzyme elevations) are mild, many other migraine and CH medications are available that do not require monitoring. In addition, VPS ER has multiple significant drug interactions. One limiting factor is that many patients do not improve with preventive treatment with one medication and other conditions such as medication overuse or affective disorders. Another limiting factor is that VPS ER is not approved for migraine in some countries and is not approved in any country for CH. Why does VPS ER seem to be helpful only to some individuals with a diagnosis of migraine or CH? The development of serious AEs, such as pancreatitis or liver problems, is unpredictable and there is no way to predict the outcome of an individual's response. The future will hopefully bring genetic and immunologic biomarkers to help predict treatment response and identify those at risk for serious AEs. The ultimate goal should be to develop preventive medication treatment that would decrease an individual's disability and headache severity while improving quality of life.

Advances in our understanding of the mechanisms or causes of migraine or CH will also lead to better treatment. Hopefully the future will bring new biomarkers, such as genetic markers, measures of brain hyperactivity, or levels of neurotransmitters, for headache disorders. The precise mechanism of how VPS ER works either for headache or epilepsy is unclear. In the upcoming years, it is hoped that diagnosing migraine and CH will be improved. Identifying the patients who require preventive treatment would also be a step in the right direction. It is important to note that migraine is not just a pain disorder, but rather a multimodal system that affects thinking, balance, and a person's sense of wellbeing.

Conclusion:

VPS ER is effective and well-tolerated in the preventive treatment of migraine and potentially helpful for many patients with CH. Clinicians should be familiar with the pharmacokinetic properties of VPS ER and be aware of potential AEs and required monitoring.

Table 1: Clinical trials of valproate formulations in migraine prophylaxis

Trial Author Date, Reference	Type of Trial	Efficacy	Dosage	Number of Patients	Reference Medication
Freitag, Collins; 2002;[53]	Randomized, double-blind, placebo-controlled, parallel-group	Mean reduction in 4-week migraine headache rate; reduction in the baseline mean from 4.4 to 1.2	500mg once daily for one week; dose then increased to 1000mg/day	237	Divalproex sodium extended-release
Hering, Kuritzky; 1992 [54]	Double blind, randomized, crossover	86.2% subjects with reduced attack frequency, severity, or duration	400mg twice per day	29	Sodium valproate
Jensen, Brinck, Olesen; 1994 [55]	Triple-blind placebo and dose-controlled, crossover study	50% reduction in migraine frequency	Dose not specified	43	Slow-release sodium valproate
Mathew, Saper, Silberstein; 1995 [57]	Randomized placebo-controlled	43% of the subjects with > 50% reduction in migraine frequency	500 to 1500mg/day	117	Divalproex sodium extended-release
Apostol, Lewis, Laforet; 2008 [58-59]	Phase 3, Open-label, multicenter study of adolescents	75% decrease in headache days but not superior to placebo	Initial dose 500mg/day, then after 15 days increased to 1000mg/day	241	Divalproex sodium extended-release
Freitag, Diamond;	Retrospective chart review	65% had improvement in	Does not specify the	138 patients	Divalproex sodium



2001 [32]	with data extraction	migraine	dosage		
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Table 2: Clinical trials of valproate formulations in cluster headache prophylaxis

Trial Author	Type of Trial	Efficacy	Dosage	Number of Patients	Reference Medication
Hering, Kuritzky; 1989 [60]	Open clinical trial	73% reported improvement	600mg to 2000mg/day in two divided doses	15	Sodium valproate
Gallagher, Mueller, Freitag; 2002 [61]	Retrospective multicenter study	73% improvement in pain	Dosage not specified	284	Divalproex sodium
El Amrani; 2002 [62]	Double-blind placebo controlled	No improvement when compared to placebo	1,000 to 2,000mg/day	96	Sodium valproate

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