

## **Disclaimer**

**The following Suggested Headache Preventative Treatment Protocol uses the Anti-Inflammatory Regimen with 10,000 IU/day vitamin D3, Omega-3 fish oil and the vitamin D3 cofactors. It was developed primarily for cluster headache sufferers, but it has also been found to be effective in preventing migraine headaches. This treatment protocol was prepared for neurologists, pain specialists, and primary care physicians who routinely treat patients with headaches. This treatment protocol is indicated for headache sufferers who have had a CT scan or MRI of the head as part of a differential diagnosis to rule out other more serious causes of head pain.**

**For others having headaches and suspect they are cluster or migraine headaches, this treatment protocol is provided for discussion purposes only.**

**If you've been diagnosed as a cluster headache sufferer or migraineur, see your PCP or neurologist, whoever is most familiar with your overall medical history and currently prescribed medications, to discuss this regimen and obtain the suggested lab tests before starting it.**



## **What is a Cluster Headache?**

A Cluster Headache is not just another headache. Saying it's just a migraine does a terrible disservice to a cluster headache sufferer although migraine headaches can be nearly as painful and just as disabling. The following narrative is all too frequently used to describe cluster headache.

Imagine, your right eye is being pried out of its socket with a screwdriver jammed through your temple into the back of your eye, or the back of your eye is being stung by a swarm of killer bees. The eyelid above that eye is beginning to swell. You start squinting, the eye is tearing and the nostril below it is running like a faucet. You are convinced there is blood pouring out of your head. The red-hot screwdriver crushing through your temple and into the eye is causing excruciating, horrible pain. You can't escape the pain and sleep is impossible so you pace from room to room, dance the cluster two-step in little circles, cry out in anguish, bang your head with your fists, fling yourself to the floor or rock in a fetal position until eventually the pain drains away.

The first few attacks come out of nowhere. You don't know what's happening, but you're convinced an artery in your brain has ruptured and death is only minutes away. Waiting for the next attack to happen is a terrible, scary feeling loaded with fear and anxiety. Sleep, when it is possible after an attack, is another source of fear. You know the attacks hit within the first hour of sleep so you sit there all night afraid to lie down. Some think they will go mad sitting there exhausted until the next attack hits and the terrible pain starts all over again.

The attacks come in clusters, an average of three a day (some experience six to eight attacks a day) for six to eight weeks a year among episodic sufferers, hence the name cluster headaches. Chronic cluster headache sufferers can experience these attacks 24 hours a day 365 days a year with very few short periods of remission that last less than a week.

The really tragic story is too many cluster headache sufferers experience these terrible attacks for years before being diagnosed. The cluster headache disorder has a prevalence of less than one tenth of one percent so even most neurologists are unfamiliar with the cluster headache syndrome and all too often assume it's some form of migraine after ruling out actual brain abnormalities with neuroimaging. There is no known cure and until now, no known cause of this disorder. Over the counter pain medications are useless and powerful opiates dull the pain, but cannot stop the attacks. Many cluster headache sufferers rate the pain of their attacks on a 10-Point Headache Pain Scale developed by "Kip" Kipple, a long time cluster headache sufferer. A Kip-1 cluster headache is minor, but they rarely stay at this pain level, escalating to a Kip-7 in less than a minute. A Kip-10 cluster headache is the most extreme. When the pain gets to a Kip-9 or Kip-10, sufferers head for the Emergency Room. Many cluster headache sufferers contemplate suicide after weeks of daily attacks numbering six to eight a day at this pain level.

A cluster headache sufferer's family is also affected by this disorder. Many family members feel helpless and confused when a loved one has a cluster headache. It's most difficult for spouses. In some cases, doing nothing or saying "I'm here if you need me" is the best course of action. An experienced Cluster Headache Supporter will frequently see a cluster headache coming before the cluster headache sufferer. An experienced Supporter will also check to see if prescribed abortives are available when they see an approaching attack and say "You're having a cluster headache, start oxygen therapy." It was the world's greatest Supporter, writing to another Supporter brand new to this nightmare, who said, "They go to a place we can't access, nor ever hope to understand".

# **Scope**

## **Disease/Condition**

**Cluster Headache**  
**Migraine Headache**

## **Guideline Category**

**Assessment of Therapeutic Effectiveness**  
**Management**  
**Prevention**  
**Treatment**  
**Discussions**

## **Clinical Specialty**

**Family Practice**  
**Internal Medicine**  
**Neurology**  
**Pharmacology**  
**Preventive Medicine**  
**Headache Pain Management**

## **Intended Users**

**Physicians**

## **Objective**

**To provide an evidence-based suggested treatment protocol for cluster headache attacks and prophylaxis of cluster headache.**

## **Target Population**

**Patients suffering from cluster headache, other TACs or migraine headache.**

# **Suggested Preventative Treatment Protocol for Neurologists, Pain Specialists, and Primary Care Physicians using the Anti-Inflammatory Regimen to Treat Patients with Cluster Headache**

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## **Background**

Treating cluster headache (CH) patients or migraineurs with the anti-inflammatory regimen of vitamin D3 and vitamin D3 cofactors to prevent their headaches represents a paradigm shift from the conventional Standards of Care Guideline recommended treatments for CH and migraines. The standards of care recommended treatments address the neurological symptoms of CH as a trigeminal autonomic cephalalgia (TAC) with neurogenic origins in the hypothalamus and manifestations in the trigeminal nerves.

Acute treatments for CH include oxygen inhalation therapy with a non-rebreathing mask at flow rates of 15 to 25 liters/minute followed by Sumatriptan Succinate (Imitrex). Subcutaneous injections of Imitrex are effective in aborting CH in 5 to 10 minutes. Imitrex nasal spray can be effective in 10 to 20 minutes. Imitrex tablets are typically effective in 20 to 30 minutes, but can take much longer.

Typical prophylactic treatments include a prednisone taper as a transitional preventative while titrating up with the longer-term preventative verapamil, a calcium channel blocker and in some cases, lithium. Greater Occipital Nerve (GON) blocks and Sphenopalatine Ganglion (SPG) blocks have also proven effective as short-term preventative treatments in some cases, but usually fade in efficacy in subsequent blockades.

The anti-inflammatory regimen with vitamin D3 and cofactors represents a completely different treatment modality that addresses vitamin and mineral deficiencies as an underlying cause or contributor of CH. That >80% of over 600 CHers respond favorably to a daily regimen of 10,000 IU/day vitamin D3, Omega-3 fatty acids and the vitamin D3 cofactors that support vitamin D3 pharmacokinetics and pharmacodynamics, suggest CH is a genetotrophic disease.

In 1956 Dr. Roger J. Williams, PhD., the biochemist who discovered the B-vitamin pantothenic acid, coined the term "genetotrophic disease" to describe diseases which resulted from genetically determined nutritional metabolic needs not being met by the individual and which result in poor gene expression. Motulsky has recently argued that many of the common degenerative diseases are the result of the imbalance nutritional intake with genetically determined needs for good health [1].

Although the anti-inflammatory regimen and treatment protocol can be categorized as complementary and alternative medicine (CAM), it should be ranked among the first treatments of choice in the standards of care recommended cluster headache interventions.

Please see your doctor to discuss the anti-inflammatory regimen and ask for the suggested lab tests before starting this regimen. If you've been on this regimen for more than 30 days and hopefully obtained a second set of suggested labs, please take the time to take the online survey of CHers taking this regimen to prevent their CH. It takes roughly 5 minutes. The results of your survey data will help strengthen the medical evidence behind the effectiveness of this CH preventative treatment protocol. You can find this survey at the following link: <http://www.esurveyspro.com/Survey.aspx?id=fb8a2415-629f-4ebc-907c-c5ce971022f6>. Please remember to press the "Submit" button when you complete it.

**Why CHers Need the Anti-Inflammatory Regimen.** Data from the online and ongoing survey of 187 CHers as of 15 April 2016, indicate 95% of CHers with active bouts of CH have a 25(OH)D serum concentration less than 47 ng/mL. These results are illustrated in Figure 1 as a normal distribution plot of baseline 25(OH)D lab results taken prior to start of the anti-inflammatory regimen. They prove the first half of the hypothesis that a vitamin D3 insufficiency/deficiency is a major determinant of the cluster headache syndrome. The fact that >80% of CHers who start this regimen experience a significant reduction in the frequency, severity and duration of their CH, or experience a pain free response as their 25(OH)D serum concentrations rise between 60 and 100 ng/mL, proves the second half of this hypothesis.

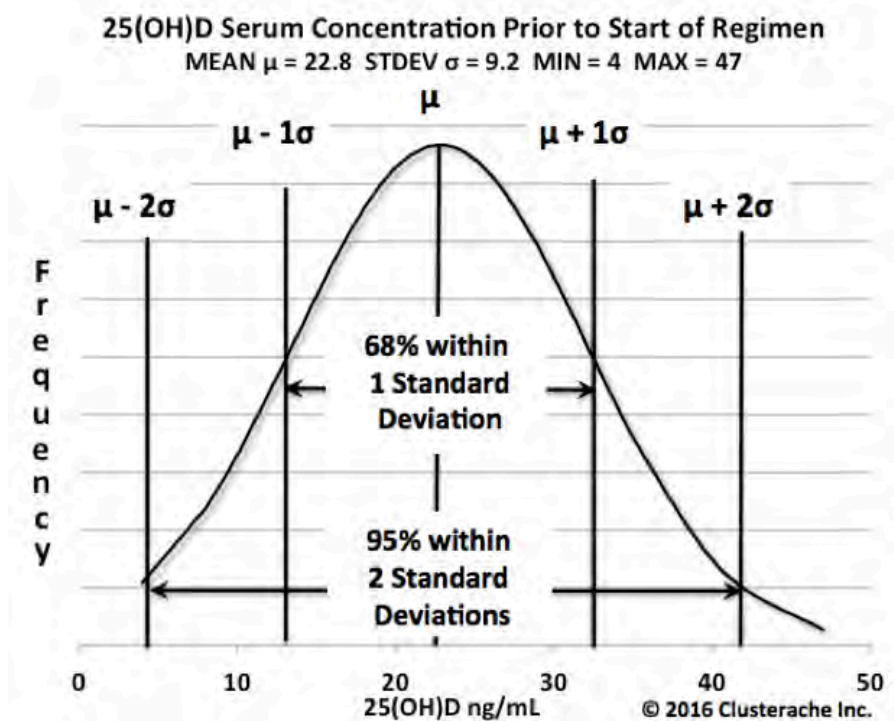


Figure 1. Normal Distribution of Baseline 25(OH)D Lab Results

**Anti-Inflammatory Regimen.** The suggested nutrients and their doses used in the Anti-Inflammatory Regimen for adults are shown in Table 1 and Figure 2 below. Children with CH should receive a vitamin D3 dose of 50 IU per pound of body weight. The other nutrients and supplements should be taken at RDA for the appropriate age group.

Table 1. Anti-Inflammatory Regimen Nutrients and Suggested Doses	
Supplement	Dose
Vitamin D3 (Cholecalciferol)	10,000 IU/day (Adjust as needed to keep serum 25(OH)D near 80 ng/mL)
Omega 3 Fish Oil	1000 to 2400 mg/day (Minimum of EPA 360 mg/day, DHA 240 mg/day)
Calcium *	220 to 500 mg/day
Magnesium	400 - 800 mg/day (magnesium chloride, glycinate or oxide)
Vitamin K2 (MK-4 & MK-7)	MK-4 1000 mcg/day, MK-7 200 mcg/day (MK-7 preferred due to half-life)
Vitamin A (Retinol) *	900 mcg (3,000 IU) for men, 700 mcg (2,333 IU) for women (Max Dose)
Vitamin B 50 Complex	3 month course, after that, 7 B vitamins in the Mature Multi will be sufficient
Zinc *	10 mg/day
Boron *	1 mg/day minimum, 3 mg/day optimum

\* Included in the Mature Multi in sufficient quantity



**Figure 2. Over-The-Counter Anti-inflammatory Regimen Nutrients**

The supplements illustrated above in Figure 2, by brand with capsule/tablet count, meet the essential nutrients and doses listed in Table 1. These supplements are available at Costco, Walmart, most supermarkets, drugstores and over the Internet at amazon.com and iherb.com. The labels on the supplements above contain the USP logo or an indication of independent laboratory testing for purity and strength of contents. A single tablet of the Mature Multi provides most of the other vitamin D3 cofactors at the required doses including calcium, zinc, boron and vitamin A (retinol). Not shown in this photo is the vitamin B 50, a single pill formulated with the seven B vitamins plus 400 mcg of folic acid. Dr. Stasha Gominak, MD, a neurologist at ETMC, Tyler, TX, suggests a 3-month course of vitamin B 50 to address any deficiencies among the seven B vitamins. The anti-inflammatory regimen can be used by itself or as an adjuvant therapy along with the Standards of Care recommended treatments for CH.

### **Patient Exam**

The following are suggested additions to normal practice neurological exams for patients with cluster headache or suspected of having cluster headache as described in the ICH Classification ICDH-II below with the following diagnostic and treatment codes.

Note: Oxygen therapy with a non-rebreathing mask at flow rates that support hyperventilation  $\geq 25$  liters/minute, is indicated as an acute treatment and abortive for patients presenting with active CH and is recommended as a first abortive of choice followed by treatment with subcutaneous triptans such as Sumatriptan Succinate (Imitrex).

IHS Classification ICHD-II - Cluster Headache - IHS 3.1, ICD-10 G44.0

Attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15-180 minutes and occurring from once every other day to 8 times a day. The attacks are associated with one or more of the following, all of which are ipsilateral: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis, eyelid oedema. Most patients are restless or agitated during an attack. If patient presents with an active CH, start oxygen therapy at 15 to 25 liters/minute with non-rebreathing oxygen mask immediately.

## **Diagnostic and Treatment Codes**

### **ICD-9-CM Diagnosis Codes:**

- Episodic Cluster Headaches – 339.01
- Chronic Cluster Headaches – 339.02

### **ICHD-II Codes:**

- Episodic Cluster Headaches – 3.1.1
- Chronic Cluster Headaches – 3.1.2

### **ICD-10 NA Codes:**

- Episodic Cluster Headaches – G44.01
- Chronic Cluster Headaches – G44.02

## **Healthcare Common Procedure Coding System (HCPCS) Codes for Home Oxygen Therapy:**

### **Equipment:**

- E0424-E0425 Stationary compressed gaseous oxygen system
- E0430-E0431 Portable gaseous oxygen system

### **Contents:**

- E0441 Oxygen contents, gaseous, 1 month's supply = 1 unit

### **Modifiers:**

- QG - Prescribed amount of oxygen is greater than four liters per minute (LPM)

Rx for home oxygen therapy should read: "Oxygen therapy at flow rate of 15 to 25 lpm with non-rebreathing mask as abortive for cluster headache. Administer STAT for 15 minutes up to 12 X per day".

## **Suggested Additions to Normal Patient Exam for Cluster Headache**

- Confirm diagnosis for cluster headache, or other trigeminal autonomic cephalalgias and primary headaches including migraine.
- Review patient history for possible insufficiencies/medical conditions that could affect vitamin D3 absorption, metabolism or lower systemic pH.
  - Hepatic
  - Renal
  - Thyroid
  - Parathyroid
  - Pancreas
  - Heart
  - Lung
  - GI Tract

- Review patient's other medical conditions including current Rx for possible drug interactions and contraindications with supplements used in the Anti-Inflammatory regimen.
  - Vitamin D3 – Hyperparathyroidism, Sarcoidosis and patients taking thiazide require close monitoring of serum and urine calcium levels.
  - Omega-3 Fish Oil – May induce a slightly lower clotting factor in some cases.
  - Calcium Supplements – May reduce bioavailability of verapamil.
  - Magnesium chloride, magnesium malate, magnesium glycinate or magnesium citrate
  - Zinc
  - Boron
  - Vitamin K2 (MK-4 & MK-7) – Vitamin K1 is contraindicated if blood thinners used.
  - Vitamin A (retinol)
  - Vitamin B 50
- Order the following lab tests to establish a baseline before starting the anti-inflammatory regimen:
  - 25-Hydroxyvitamin D3 [25(OH)D3]. CPT Code 82306. Quest Diagnostics Test Name: 92888-QuestAssured 25-OH Vitamin D (Total), LC/MS/MS. 95% of CHers with active bouts of cluster headache will have a 25(OH)D serum concentration  $\leq 47$  ng/mL, (117.2 nmol/L). Any 25(OH)D serum concentration  $< 50$  ng/mL, (125 nmol/L) is grounds for starting this regimen.
  - Vitamin B12 (Cobalamin). CPT Code 82607
  - Parathyroid Hormone (PTH) Intact and Total Calcium. CPT codes 83970, 82310. Establish baseline.
  - CBC (w/ Differential and Platelets). CPT Code 85025. (Abs) Eos  $>350$  indicates possible allergy
  - Eosinophil Count, Nasal. CPT Code 89190
  - Lab results for Erythrocyte Sedimentation Rate (ESR) CPT Code 85652, C-Reactive Protein (CRP) CPT Code 86140 and plasma viscosity may prove useful if inflammation is suspected

**Comorbid Conditions Requiring Special Attention.** Allergies, infections, pregnancy and lactation have been found to affect the pathogenesis of cluster headache. Allergies trigger inflammation and an immune system response that have the capacity to override the CH preventative effects of vitamin D3. CH attacks during pregnancy and lactation draw questions, in particular, as to the best way to treat CH when they occur. Fortunately, this vitamin D3 therapy is very safe during pregnancy and lactation.

**Allergies.** If indications of an allergy are present or the absolute eosinophil count is in excess of 350, treatment with a first-generation antihistamine like Benadryl (Diphenhydramine hydrochloride) in addition to the anti-inflammatory regimen has proven effective in preventing CH. First-generation antihistamines pass through the blood brain barrier to block histamine H1 receptors on nerve cells throughout the brain and in particular, the hypothalamus and trigeminal ganglia where production of calcitonin gene-related peptide (CGRP) and Substance P are highest. Second- and third-generation antihistamines cannot do this.

When neurons within the hypothalamus and trigeminal ganglia are insulted by histamine from an allergic reaction, this triggers the release of CGRP and Substance P. Although both are implicated in the cluster headache pathogenesis, CGRP has been found to trigger rapid neurogenic inflammation and the severe pain associated with CH.



The term ‘neurogenic inflammation’ has been adopted to describe the local release of inflammatory mediators, such as substance P and CGRP, from neurons. Once released, these neuropeptides induce the release of histamine from adjacent mast cells through paracrine signaling. In turn, histamine evokes the release of substance P and CGRP; thus, establishing a bidirectional link between histamine and these neuropeptides during neurogenic inflammation [2].

What all this means is a simple allergic reaction can trigger a chain reaction and self-sustaining perfect storm within the brain producing more CGRP and Substance P than can be down-regulated or suppressed by vitamin D3... hence no response or at best, only a limited response to the anti-inflammatory regimen. In other words, a CHER suffering from an allergy whether obvious or sub-clinical (no outward or obvious symptoms) may become refractory to the anti-inflammatory regimen's capacity to prevent CH. This same mechanism likely accounts for the CHER being refractory to most other CH prophylaxis and likely makes oxygen therapy less effective with longer abort times.

The addition of Benadryl (Diphenhydramine hydrochloride) halts this chain reaction by blocking histamine H1 receptors on neurons within the hypothalamus and trigeminal ganglia that are the largest producers of CGRP and Substance P.

The bottom line is the simple addition of Benadryl (Diphenhydramine hydrochloride) means many of the 18% of CHERs who don't respond to the anti-inflammatory regimen or have a partial response within the first two weeks of treatment, start responding with more CH pain free days and nights.

50 mg/day (25 mg twice a day or 50 mg at bed time) Benadryl plus additional vitamin D3 up to 50,000 IU/day may be required to maintain a CH pain free response during periods of high pollen count resulting in an allergic reaction. Caution patient that Benadryl (Diphenhydramine hydrochloride) can and will cause drowsiness and not to drive when taking it if at all possible. Some CHERs have reported that 12.5 mg Children's Allergy Relief Liquid Benadryl taken twice a day is also very effective with less drowsiness.

Based on the current body of evidence, which are large, first-generation antihistamines are not associated with an increased risk of malformations or any other adverse fetal effects when taken during pregnancy. In addition, none of the first-generation antihistamines are excreted in the breast milk in an appreciable amount so as to have any adverse effects on the breastfeeding infant. Therefore, pregnant and breastfeeding women can be reassured that they can help alleviate their CH symptoms by adding Benadryl to this regimen without posing an increased risk to their fetuses or breastfeeding infants [3].

**Infections.** Viral and bacterial infections trigger an immune response that increases the demand for vitamin D3, 25(OH)D and 1,25(OH)2D3. This increased demand creates a supply and demand imbalance leaving too little vitamin D3 or 25(OH)D serum concentrations available at the cellular level to prevent CH. Several CHERs have reported falling out of a sustained remission following the onset of an infection after months of vitamin D3 at a dose of 10,000 IU/day and a serum 25(OH)D concentrations near 80 ng/mL (200 nmol/L). If an infection is suspected during the physical exam, advise the CHER that the 2-Week or 4-Week vitamin D3 loading schedule will help and that a favorable response could take longer if neither loading schedule is used. Bacterial infections that require treatment with an antibiotic create an additional problem.

Antibiotics are indiscriminate, so kill off the friendly colonies of biota living in our GI tract and respiratory passages called the microbiome along with the targeted pathogenic bacterial organisms. The human microbiome is the ecological community of commensal, symbiotic and pathogenic

microorganisms that inhabit the GI tract and respiratory passages. As the colonies of friendly biota make up most of our immune system, they need to be reseeded and replaced when antibiotics are indicated. The suggested course of action is to take a high concentration probiotic capsule 12 hours after the oral antibiotic and to continue taking the probiotic until the bottle is completely empty.

**Pregnancy and Lactation** None of the micronutrients in the anti-inflammatory regimen carry contraindications during pregnancy or lactation. Moreover, the prevailing medical evidence from RCTs over the last five years indicate the physiological need for the micronutrients in the anti-inflammatory regimen are greatest during pregnancy and lactation. This begs the question, how much of each is sufficient and is more beneficial? A peer review of the Institute of Medicine (IOM) Food and Nutrition Board (FNB) recommended RDA for vitamin D3 found 600 IU/day was clearly insufficient during pregnancy and lactation.

The consensus among leading experts in vitamin D3 nutrition indicates 6000 IU/day is the minimum dose during pregnancy. CH during pregnancy and lactation represent special cases with respect to vitamin D3 dosing. Although data collected from pregnant CHers taking the anti-inflammatory regimen with 10,000 IU/day vitamin D3 are limited, all reported normal, full-term births of healthy babies without complications.

One case study in particular, involved a 40-year-old woman who had taken the anti-inflammatory regimen for over three years prior to her first pregnancy. She was taking this regimen for its health benefits as she was not a CHer. Her OB was concerned at first about her taking 10,000 IU/day vitamin D3 during pregnancy. However, after three consecutive sets of lab tests for her serum 25(OH)D, total calcium and PTH all came back within their normal reference ranges, coupled with a flawless pregnancy and full-term delivery of a very healthy baby, he now suggests this regimen to all his expectant mothers. Her average 25(OH)D serum concentration from these lab tests was 80 ng/mL, (200 nmol/L).

A second case study of pregnancy and CH involved a 45-year-old woman, episodic CH since she was 34, and not diagnosed with CH until she was 39. She started the anti-inflammatory regimen in April of 2013 seeing her PCP for frequent lab tests of her serum 25(OH)D, calcium and PTH. She continued the anti-inflammatory regimen throughout her pregnancy to prevent her CH and as a health aid. She gave birth to a full term, very healthy, 8 lb. 4 oz. son in November of 2015. 25(OH)D lab tests on maternal and cord blood done at the time of birth revealed a maternal 25(OH)D serum concentration of 64.71 ng/mL and the cord blood 25(OH)D concentration of 34.37 ng/mL.

### **Suggested vitamin D3 dosing strategies and follow up diagnostic lab tests**

**Normal Dosing Interval and Duration.** Start the anti-inflammatory regimen at 10,000 IU/day vitamin D3 (liquid softgel capsules), the Omega-3 fish oil, and the rest of the cofactor nutrients listed in Table 1 or Figure 1. This is the normal daily maintenance dose for episodic and chronic CHers. Daily dosing with vitamin D3 helps ensure the highest possible vitamin D3 serum concentration throughout the day and a relatively constant 25(OH)D serum concentration. This is important as both vitamin D3 and 25(OH)D enter cells throughout the periphery and brain where they are hydroxylated to 1,25(OH)<sub>2</sub>D3 in order to support autocrine/paracrine signaling and genetic expression. Accordingly, a missed dose of vitamin D3 should be taken as soon as possible. Staying hydrated is also important. Advise the patient to drink at least 2 liters of water a day.

Chronic CHers will need to stay on this regimen year-round. It's advisable that episodic CHers remain on this regimen year round as well to avoid painful delays in rebuilding 25(OH)D serum concentrations

at the start of subsequent CH cycles. It is also advisable to start the 3-month course of vitamin B 50 at this time. A year's worth of the nutrients in this daily regimen costs less than two shots of Imitrex.

Order lab tests for 25(OH)D at 3 months and 6 months after start of this regimen. As the 25(OH)D response to dose of vitamin D3 varies between individuals, adjust the vitamin D3 dose to keep serum 25(OH)D close to 80 ng/mL, (200 nmol/L). Annual labs for 25(OH)D can be conducted after the first year. The normal, expected response to this regimen will include a serum total calcium concentration within its normal reference range and PTH at the low end of its normal reference range.

**Vitamin D3 Loading (Repletion) For CHers with Low Serum 25(OH)D Concentrations** If the initial 25(OH)D lab test indicates  $\leq 30$  ng/mL, (75 nmol/l), start the 12-day, 2-week or 4-week accelerated vitamin D3 loading schedule. These vitamin D3 loading schedules involve taking a total loading dose of 600,000 IU of vitamin D3 over 12-days, a 2-weeks or 4-weeks with an average 25(OH)D response (gain) of 60 ng/mL on top of the starting serum concentration. Start the anti-inflammatory regimen at 10,000 IU/day vitamin D3 plus the Omega-3 fish oil and the vitamin D3 cofactors. Continue at this dose for up to two days to ensure no reaction to the vitamin D3 or other supplements. Allergic reactions to vitamin D3 are very rare. People with known allergic reactions to wool or sunlight should be tested at much lower initial doses of vitamin D3. If no allergic reaction is present start either the two-week or four-week vitamin D3 loading schedules as detailed in the following.

#### **12-Day Vitamin D3 Loading Schedule**

Take 50,000 IU/day vitamin D3 for 12 days then drop the dose to 10,000, your initial maintenance dose

#### **Two-Week Vitamin D3 Loading Schedule**

Week 1. 50,000 IU/day vitamin D3 for one week. Take all the other supplements

Week 2. 40,000 IU/day vitamin D3 for six (6) days then drop the vitamin D3 dose to 10,000 IU/day on the 7<sup>th</sup> day. This will be the normal maintenance dose of vitamin D3. Take all the other supplements and cofactors daily.

#### **Four-Week Vitamin D3 Loading Schedule**

Week 1. 20,000 IU/day vitamin D3 plus one (1) loading dose of 50,000 IU/week vitamin D3

Week 2. 20,000 IU/day vitamin D3 plus one (1) loading dose of 50,000 IU/week vitamin D3

Week 3. 15,000 IU/day vitamin D3 and no loading dose

Week 4. 15,000 IU/day vitamin D3 and no loading dose

Take all the other supplements and cofactors daily. At the end of the 4<sup>th</sup> week, drop the vitamin D3 dose to 10,000 IU/day plus the other supplements and cofactors.

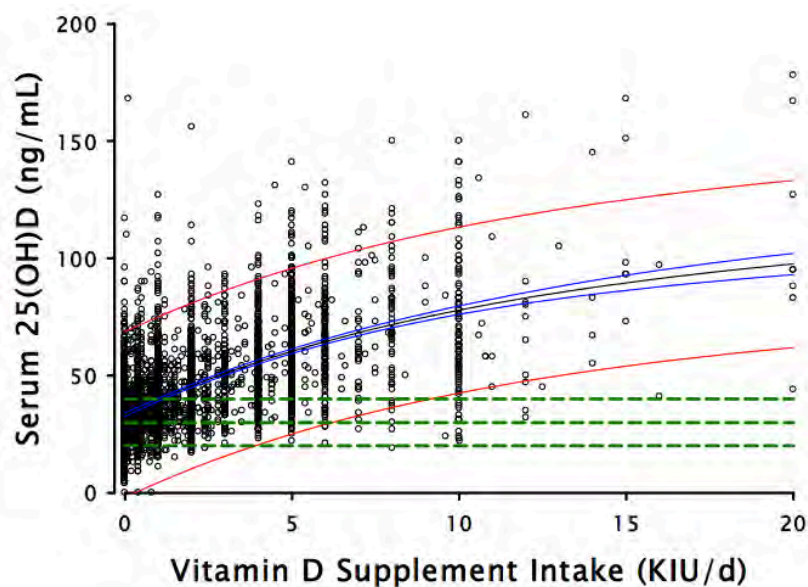
These three vitamin D3 loading schedules are safe, equally effective with the 12-day loading schedule the fastest and should result in a rapid 25(OH)D response to therapeutic concentrations near 80 ng/mL with a significant reduction in the frequency, severity and duration of CH faster than at the maintenance dose 10,000 IU/day vitamin D3.

The initial target serum concentration for 25(OH)D is 80 ng/mL. The total loading dose can be adjusted at the rate of 100,000 IU vitamin D3 per 10 ng/mL of 25(OH)D response. Vitamin D3 is lipophilic so adjustments can also be made for BMI. If the BMI is in the normal range 18.5 to 25, use a total vitamin D3 loading dose of 600,000 IU. If the BMI is  $<18.5$ , subtract 100,000 IU from the total loading dose. If the BMI is  $\geq 25$ , add 100,000 to the total loading dose.

Lab tests for serum 25(OH)D, calcium and PTH can be conducted 3 weeks after completion any of the loading schedules. Results should indicate a 60 ng/mL gain above the 25(OH)D baseline/starting serum concentration. Another set of lab tests of serum 25(OH)D, calcium and PTH should be conducted three months after start of regimen while on the same 10,000 IU/day maintenance dose. This should provide sufficient time for the 25(OH)D response to the maintenance dose of vitamin D3 to reach a stable equilibrium. Adjustments to the vitamin D3 maintenance dose can be made at this time to maintain a target 25(OH)D serum concentration of 80 ng/mL, (200 nmol/L). Routine follow up lab tests for serum 25(OH)D, total calcium and PTH should be done on a yearly basis after that. Don't be concerned if the 25(OH)D lab test result comes back over 100 ng/mL. 25(OH)D is a poor indicator of vitamin D3 intoxication/toxicity. The actual 25(OH)D concentration associated with vitamin D3 intoxication/toxicity is well over 200 ng/mL (500 nmol/L) The only real indication of vitamin D3 toxicity is a serum total calcium concentration greater than 10.5 mg/dL and a low PTH less than 20 pg/mL.

**Vitamin D3 Maintenance Dose.** The maintenance dose of 10,000 IU/day for adults was selected for a number of reasons. The first is continuous, long-term doses of 10,000 IU/day vitamin D3 have been found to be safe with no evidence of hypercalcemia or hypercalciuria by a significant number of well constructed and adequately powered clinical studies [4]. The second reason deals with variations in 25(OH)D response to dose of vitamin D3 between individuals and variations in 25(OH)D response due to comorbid conditions. Finally, as the average adult can generate 10,000 IU of cutaneous vitamin D3 in as little as 10 to 30 minutes with whole body exposure to the UV B in direct midday summer sun without sun block depending on skin type, 10,000 IU/day vitamin D3 represents a physiological dose rather than being considered a pharmacological dose.

If the 3-month lab test for 25(OH)D comes back < 60 ng/mL (150 nmol/L) or > 100 ng/mL (250 nmol/L) adjust the vitamin D3 maintenance dose accordingly using 50 IU per pound (110 IU per Kg) of body weight per day as an initial dosing guide then test again in another 3 months. The GrassRootsHealth D\* Action survey results from 2015 totaling over 6334 people taking vitamin D3 at various doses with regular 25(OH)D lab tests every 6 months found that 96% of the 1,600 participants taking 10,000 IU/day vitamin D3 achieved a 25(OH)D serum concentration of 40 ng/ml or greater are illustrated in Figure 3, used with permission.



**Figure 3. Serum 25(OH)D plotted against vitamin D supplement intake**

**Dosing Interval and Time of Administration.** Whether from oral supplements or dietary sources, vitamin D3 enters the bloodstream where most of it binds with the vitamin D binding protein (VDBP), a protein that carries vitamin D and its metabolites throughout the circulatory system. As serum vitamin D3 is hydroxylated to 25(OH)D3 each time it passes through the liver, its serum concentration drops rapidly resulting in a serum half-life of 24 to 36 hours. That makes a daily intake of vitamin D3 the optimum dosing interval. The daily intake of vitamin D3 helps ensure an adequate serum concentration after “first pass” through the liver as it is clear from the initial response times to this regimen, measured in hours in many cases, that vitamin D3 is also entering target neurons within the brain along with 25(OH)D3, where sufficient enzymes are present to hydroxylate vitamin D3 to 25(OH)D3 and on to 1,25(OH)2D3, the active hormonal form of vitamin D3 that’s responsible for genetic expression and autocrine signaling. This regimen should be taken with the largest meal of the day containing the most fats. This helps ensure optimum absorption and minimizes GI tract problems.

**Missed Doses.** The maintenance of serum concentrations of 25(OH)D is directly related to vitamin D3 intake. Although the daily intake of vitamin D3 maintenance dose ensures optimum serum concentrations of vitamin D3 and its first metabolite 25(OH)D, several RCTs have shown weekly dosing is just as effective in maintaining optimum and stable 25(OH)D serum concentrations. Accordingly, if a dose of vitamin D3 is missed, it should be taken with the next regular dose.

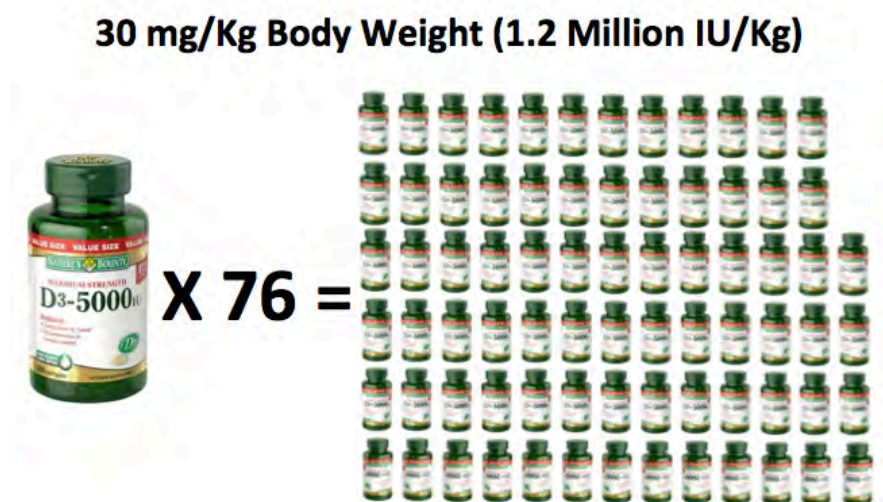
**What to do if CH symptoms continue with serum 25(OH)D around 80 ng/mL.** Some CHers may require a higher maintenance dose >10,000 IU/day vitamin D3 and a higher serum 25(OH)D response >80 ng/mL to achieve a CH pain free response. If this happens, titrate the maintenance dose up by 5,000 IU every two days to a maximum of 40,000 IU/day. Advise the patient that it is essential to maintain hydration by drinking 2 to 2.5 liters of water/24 hours at vitamin D3 doses  $\geq 15,000$  IU/day. If the CHer experiences a favorable response between 15,000 IU/day and 40,000 IU/day, advise the patient to stay at that dose for at least a month then come in for labs of serum 25(OH)D, total calcium, PTH and BUN/Creatinine Ratio. As long as serum calcium stays within its normal reference range, PTH is low and the BUN/Creatinine Ratio is normal, the CH’er can stay at this new maintenance dose, but should come in for these same labs again at 6 months or one year.

Some assay methods for serum 25(OH)D have an upper reporting range of 150 to 164 ng/mL. The Quest Diagnostics QuestAssureD™ 25-Hydroxyvitamin D (D2, D3), LC/MS/MS, Test Number (92888), has reportable ranges of 4-512 ng/mL for 25(OH)D2, 4-512 ng/mL for 25(OH)D3 and 4-1024 ng/mL for total 25(OH)D.

**Vitamin D3 Safety and Toxicity.** Vitamin D3 is without a doubt, one of the safest nutrient we can take. In the history of the FDA's Adverse Events Reporting System (FAERS), there has yet to be a single death attributed to vitamin D3. However, too much vitamin D3 just like too much table salt or too much water can be toxic. That said, it takes a lot of vitamin D3 to induce a toxic response as measured by serum and urine calcium concentrations. Moreover, it's not the vitamin D3 dose or the resulting 25(OH)D serum concentration response that counts. A 25(OH)D serum concentration greater than 100 ng/mL or even 200 ng/mL by itself, is not an indication of vitamin D3 intoxication/hypervitaminosis D.

A total calcium serum concentration above its normal reference range of 8.5 to 10.5 mg/dL is one of the only valid indications of hypercalcemia hence vitamin D3 toxicity. Accordingly, if the total calcium serum concentration is 10.5 ng/dL, test for urine calcium and if it remains within its normal reference range, advise the CHer to lower the vitamin D3 intake and come in for another round of labs in a month to ensure serum calcium remains within its normal reference range. If the total calcium serum concentration is significantly above 10.5 mg/dL, advise the patient to stop vitamin D3 intake for a month, continue hydration at 2 to 2.5 liters of water/24 hours and retest before resuming at a lower vitamin D3 intake.

There are frequent references in open source literature to the use of vitamin D3 as a rodenticide. While it's true that vitamin D3 has been used as a rodenticide, so has warfarin a.k.a. Coumadin, the blood thinner. The amount of vitamin D3 that must be consumed by the common house rat to achieve an LD<sub>50</sub> defined as the amount needed for half of the rats taking this dose to die, amounts to 30 mg of vitamin D3/Kg of body weight (1.2 Million IU vitamin D3/Kg) per day. Assuming this same LD<sub>50</sub> rat model applies to humans, a 95 Kg adult would need to consume 114 Million IU of vitamin D3 to reach an LD<sub>50</sub> dose. The following chart in Figure 4 illustrates a graphic display of this dose in terms of 300 count bottles of 5,000 IU liquid soft gel vitamin D3 capsules that would need to be consumed in one day.



**Figure 4. Vitamin D3 LD<sub>50</sub> for a 95 Kg Adult**

**Additional Beneficial Supplements.** Additional supplements that have been found to improve the headache pain free response include Curcumin (Turmeric) at 400 - 500 mg/day (with food), Vitamin C (Ascorbic Acid) at 6,000 mg/day (1000 mg every 2 hours) and a tablet a day of Coenzyme Q10 (CoQ10). Under normal conditions, an otherwise healthy adult needs 1,000 - 2,000 mg/day vitamin C. Daily vitamin C is important for cardiovascular health as humans lost the genetic capacity to synthesize it so we need adequate vitamin C from dietary or supplemental sources. It's very interesting to note that scurvy, cardiovascular disease and heart attacks do not occur in most animals as they can make their own vitamin C. However, humans and other primates (the simians—monkeys and apes—and tarsiers), guinea pigs, most bats, and some species of birds and fish lack an enzyme (L-gulonolactone oxidase) necessary for vitamin C synthesis so must obtain it daily from dietary sources or supplements. That's a real thinker.

If antibiotics have been prescribed for a bacterial infection, a course of probiotics is indicated as antibiotics are indiscriminant and will destroy friendly symbiotic colonies of bacteria and biota called the microbiome, living in the GI tract. Separating the doses of antibiotic and probiotic by 12 hours allows for a sufficient physiological response to each without impacting their respective therapeutic effects. The course of probiotics should be continued for at least a month after the course of antibiotics has completed.

Coenzyme Q10 (CoQ10) has been indicated for migraineurs as concluded by PS et al., in the RCT titled: Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial, *Neurology*. 2005 Feb 22;64(4):713-5, which reported: "We compared CoQ10 (3 x 100 mg/day) and placebo in 42 migraine patients in a double-blind, randomized, placebo-controlled trial. CoQ10 was superior to placebo for attack-frequency, headache-days and days-with-nausea in the third treatment month and well tolerated; 50%-responder-rate for attack frequency was 14.4% for placebo and 47.6% for CoQ10 (number-needed-to-treat: 3). CoQ10 is efficacious and well tolerated." If the CHer is over 35 and in particular, if taking statins, daily CoQ10 is indicated to provide additional relief from CH symptoms as well as guard against adverse statin side effects.

**Diet.** In keeping with the holistic approach to preventing cluster and migraine headache, there are dietary considerations that also apply to headache prevention as well as overall health. Contrary to dietary recommendations by the American Medical Association and the American Heart Association, cholesterol is good for us. Moreover, the real medical evidence is finally coming to light that statins are not. That means diets containing cholesterol, such as eggs, meats, and saturated fats like butter, bacon fat and lard as well as olive oil and coconut oil are actually good for us in moderation. There was a recent article about a 117-year-old woman in Italy who has eaten two raw eggs a day for the last 90 years. That blows big holes in the cholesterol myth that started with President Eisenhower in 1953, when junk science was used to link his heart attack to cholesterol and resulted in the rise of life-long statin prescriptions.

There are several very healthy diets and most of them call for fresh whole foods and the avoidance of off-the-shelf mass-produced meals. One of the healthiest diets is called GOMBS, the acronym for Greens, Onions, Mushrooms, Beans & berries and Seeds & nuts. Adding grass-fed beef, lamb, pork, free-range poultry and wild salmon are excellent additions to the GOMBS diet. Restricting gluten, carbohydrate and sugar intake and in particular eliminating high fructose corn syrup (HFCS) are also important dietary considerations. Sugars and HFCS stimulate cardiovascular inflammation, one of the real culprits resulting in cardiovascular disease.



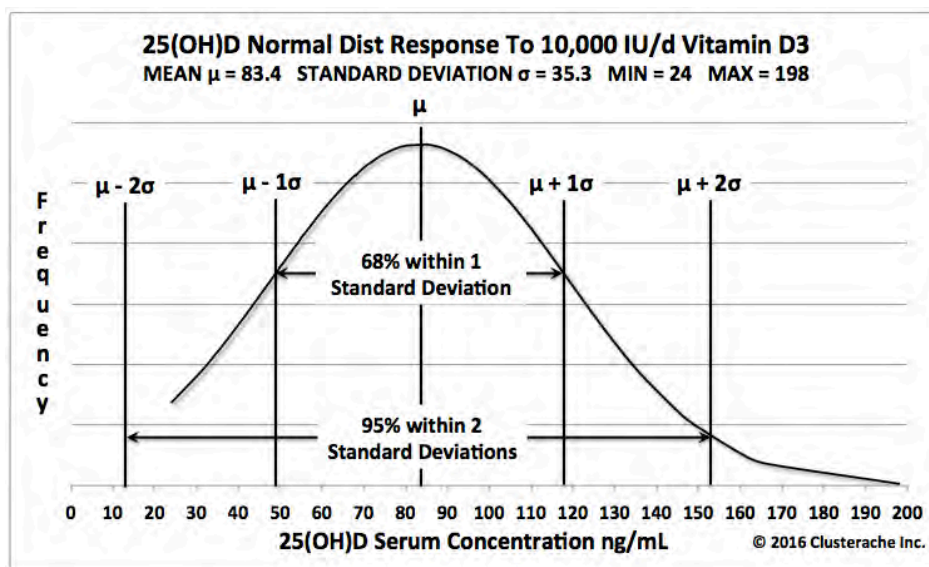
## What To Expect

Data from the ongoing online survey of CHers taking the anti-inflammatory regimen to prevent their CH are summarized below in the following tables and charts. The primary outcome measure is a favorable response with a 70% reduction in CH frequency in  $\leq 30$  days. The secondary outcome measure is a complete cessation of CH in  $\leq 30$  days.

Between 13 December 2011 and 15 April 2016, 280 participants started the online survey. 187 participants completed required questions and submitted. Survey data from these 187 participants indicate an aggregate raw efficacy of 81.3% with 152 participants achieving greater than a 70% reduction in the frequency of their CH within the first 30 days. Table 2 below provides a summary of survey participant demographic and clinical characteristics for the CH phenotype.

<b>Table 2. Survey Participant Demographic and Clinical Characteristics</b>	All n=187	Episodic	Chronic
Current Age Mean, SD, [range]	44, 11, [25-85]	44	45
Gender, M/F, [ratio], (%/%)	146/41 [3.6:1], (78/22)	103/32	43/9
Episodic/Chronic [ratio], (%/%)	136/51 [2.7:1], (73/27)	136	51
Mean Years with CH, SD, [range]	16.6, 10.4, [1-46]	17.5	14.1
Mean Baseline 25(OH)D ng/mL, SD, [range]	22.8, 9.2, [4-41]	22.8	22.8
Mean After 25(OH)D ng/mL, SD, [range]	83.4, 35.3, [24-198] p<.0001	79.2	95.5
Favorable Response w/in 30 days, n, (%)	152, (81.3%)	120, (87.0%)	32, (62.7%)
Pain Free Response w/in 30 days, n, (%)	102, (54.5%)	79, (58.1%)	22, (43.1%)

The following chart illustrated in Figure 5. plots the normal distribution of 25(OH)D lab tests results reported by survey participants after taking the Anti-Inflammatory Regimen at a vitamin D3 maintenance dose of 10,000 IU/day for  $\geq 30$  days.

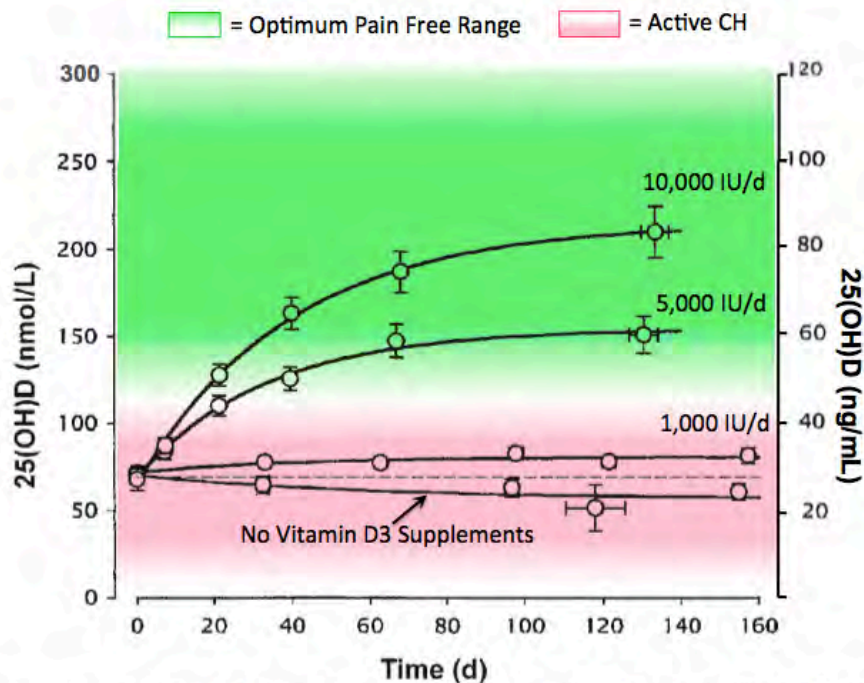


**Figure 5. Serum 25(OH)D Normal Distribution Response to 10,000 IU/day Vitamin D3**

Figure 6 illustrates a chart developed by Dr. Robert Heaney, MD, Professor Emeritus, Creighton University School of Medicine. It illustrates the average time course 25(OH)D response to extended vitamin D3 doses of 1,000 IU/day, 5,000 IU/day and 10,000 IU/day. The color bands overlaid on this chart represent 25(OH)D serum concentration ranges and cluster headache status reported by survey



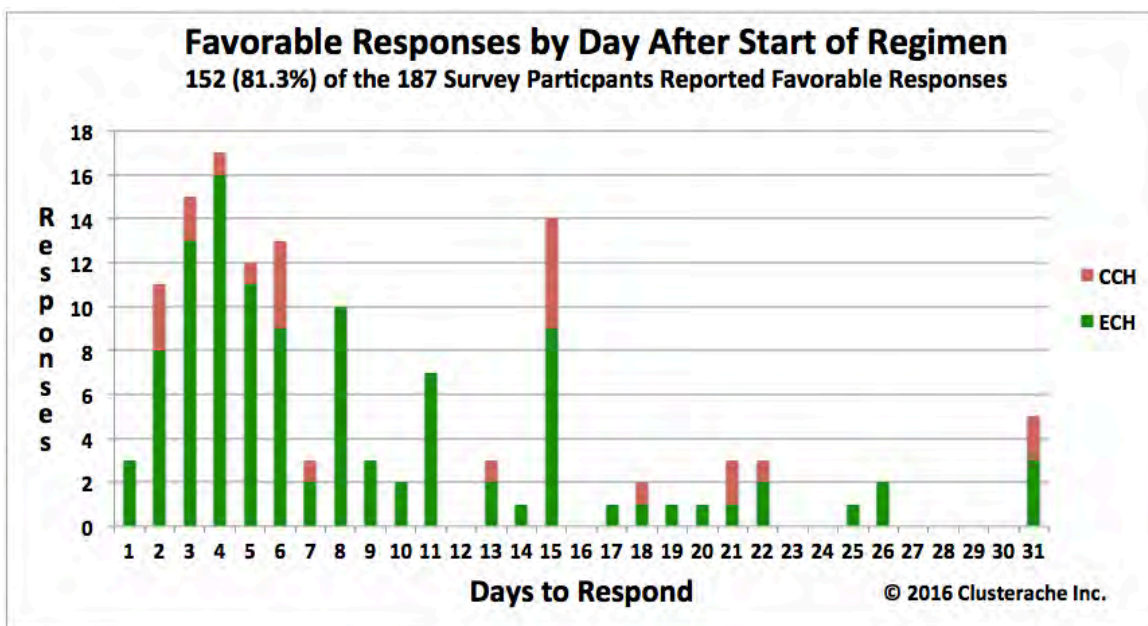
participants before and after starting the anti-inflammatory regimen. The Optimum pain free range shown in green approximates a one-sigma ( $1\sigma$ ) Standard Deviation range about a mean 25(OH)D serum concentration of 83.4 ng/mL, (208.5 nmol/L).



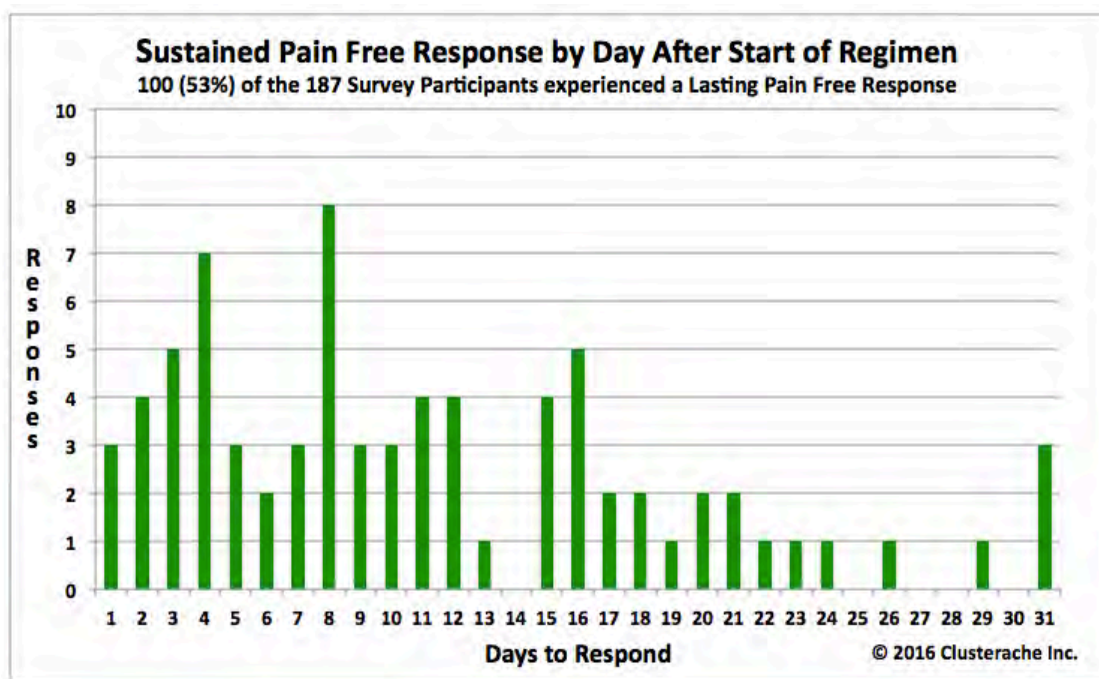
Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol  
 Robert P Heaney, K Michael Davies, Tai C Chen, Michael F Holick, and M Janet Barger-Lux  
 Am J Clin Nutr 2003;77:204–10. Printed in USA. © 2003 American Society for Clinical Nutrition

**Figure 6. Average 25(OH)D Time Course Response and CH Response to Vitamin D3**

Figure 7 illustrates the favorable responses to this regimen by day after start of regimen and Figure 8 illustrates sustained pain free responses by day after start of regimen.



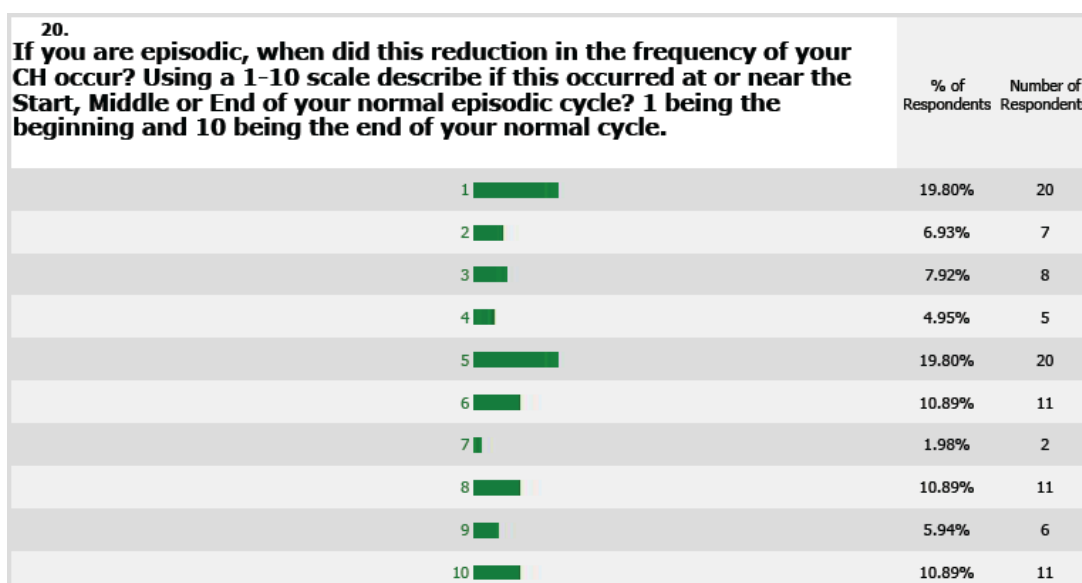
**Figure 7. Days to a favorable response from start of regimen**



**Figure 8. Days to sustained pain free response from start of regimen**

Even with a raw average efficacy of 81% for episodic and chronic CHers, the actual efficacy of this regimen to affect a significant reduction in the frequency, severity and duration of CH within the first 30 days is likely closer to 72%. This is due to the confounding factor of episodic CHers confusing efficacy of this regimen with end of CH cycle. This confounding factor has yet to be discussed or accounted for in RCTs of CH preventatives sponsored by the pharmaceutical companies.

We attempted to quantify the magnitude of this confounding factor in the online survey, by asking episodic CHers, when, in the course of their average episodic cycle, they experienced a favorable response. The Figure 9 illustrates the results of this survey question. You be the judge.



**Figure 9. Confounding Factor - Confusing Favorable Response with End of Cycle**

**Limitations.** Although the anti-inflammatory regimen is a safe and effective cluster headache preventative that can be taken with other standards of care recommended CH medications, it is not a cure. Chronic CHers who experience a sustained pain free response to this regimen will experience a recurrence of cluster headache symptoms in as little as a week after stopping this regimen. Episodic CHers who stop this regimen after their current episodic bout of CH ends, will experience a recurrence of cluster headache when the next cycle comes around. The majority of episodic CHers who have stayed on this regimen for more than a year and some up to four years, have reported sailing through their normal cluster headache cycle periods completely CH pain free.

**Safety.** There have been no instances of vitamin D3 intoxication reported over the last five years since cluster headache sufferers started using this regimen to prevent their CH and no adverse events that required medical attention. A handful of CHers under physician's supervision, have reported sustained serum 25(OH)D concentrations above 100 ng/mL, (250 nmol/L) some as high as 198 ng/mL. They also reported total calcium serum concentrations were within normal reference ranges and PTH concentrations at the low end of the reporting range with no other symptoms other than a cessation of their CH.

It's interesting to note that a compilation of vitamin D studies conducted by Dr. Reinhold Vieth in 1999 titled *Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety* cited 10 studies where subjects were reported as intoxicated with vitamin D due to overdose with serum 25(OH)D concentrations averaging 700 to 1000 nmol/L. Most involved vitamin D2 (ergocalciferol) at doses  $\geq$  50,000 IU/day for periods of 12 weeks up to a year.

**Adverse Side Effects.** The anti-inflammatory regimen is generally well tolerated, but some minor side effects do occur. These are usually associated with GI tract discomfort from the Omega-3 Fish Oil and/or osmotic diarrhea from the magnesium. Taking magnesium chloride, magnesium malate, magnesium glycinate or magnesium oxide can lower the incidence of osmotic diarrhea and improve magnesium bioavailability. Taking half the daily magnesium with breakfast and the other half with the evening meal also helps prevent osmotic diarrhea.

Up to 5% of CHers using the anti-inflammatory regimen reported an initial increase in the frequency and severity of their CH during the first few days after starting treatment. If this happens, stop the entire regimen for two days, then restart with just 10,000 IU/day vitamin D3 for another two days to make sure the reaction was not due to vitamin D3. Add the magnesium supplements next, then wait two days to ensure no reaction. Continue adding the supplements in two-day intervals using the process of elimination to determine what was causing the reaction.

Several CHers reported a recurrence of CH symptoms after experiencing viral or bacterial infections, i.e., colds or flu, trauma and surgery. Allergic reactions are also a problem. All these conditions trigger an immune response that can dramatically increase inflammation with a concomitant decrease in 25-Hydroxy Vitamin D3 serum concentrations. If patients have had a recent course of antibiotics or are presently taking antibiotics, suggest starting a probiotic to help replace friendly colonies of bacteria in the human microbiome that were destroyed by the antibiotic.

### **Comorbid Conditions That Affect The Efficacy of Vitamin D3 As A CH Preventative**

- **Allergic Reactions.** Reports from CHers taking the anti-inflammatory regimen indicate allergic reactions interfere with vitamin D3 as a CH preventative. If an allergic reaction is suspect from

the physical exam or as indicated by an absolute eosinophil count in excess of 350, treat with a first-generation antihistamine such as (Diphenhydramine hydrochloride). First-generation antihistamines pass through the blood brain barrier to block histamine H1 receptors in the brain cells. Second- and third-generation antihistamines cannot do this. The suggested adult dose of a single 25 mg tablet every 12 hours has proven effective in reducing the allergy symptoms and enabling the vitamin D3 preventative effect. Several CHers have reported 12.5 mg Children's Allergy Relief (Liquid Benadryl) taken twice a day is also very effective with less drowsiness. A 7- to 10-day course of Benadryl (Diphenhydramine hydrochloride) should be sufficient in most cases. However if the allergen source is still elevated, a 2-week course of Benadryl may be required. Available literature on H1 histamine blockers indicate a single bedtime dose achieves almost as good results as divided doses. Diphenhydramine hydrochloride is a mild CNS depressant, so advise patients taking it not to drive if at all possible. If they do need to drive during the day, suggest taking it after driving home for the day.

- **Infections, Viral and Bacterial.** Viral and bacterial infections trigger the body's immune system into action. Inflammation is one of the first reactions as it increases the flow of blood containing antiviral and antibacterial agents to the infected area. One of the functions of vitamin D is to promote the differentiation of monocytes into macrophages, dendritic cells, and lymphocytes. These cells represent the first line of defense of the nonspecific immune system and play an important role in infection control. The interaction of vitamin D with the immune system is one of its most well-known effects.

The active vitamin D3 metabolite, 1,25(OH)<sub>2</sub>D<sub>3</sub> regulates innate and adaptive immune system, because its receptors are widely present on many immune cells, such as macrophages, dendritic cells, T cells, and B cells. Vitamin D is thought to be able to activate cathelicidins, antimicrobial peptides present within the lysosomes of macrophages, and polymorphonuclear leukocytes. The bottom line is infections trigger an immune response that competes for available vitamin D3 and its metabolites. This competition can leave insufficient vitamin D3 available to prevent CH. A good rule of thumb when symptoms of a cold or flu present is to start taking a 50,000 IU/day loading dose of vitamin D3 for five to seven days before dropping back to the 10,000 IU/day vitamin D3 maintenance dose.

- **Surgery and Trauma.** Surgery and trauma trigger inflammation around the wound to increase the flow of blood containing immune system macrophages, dendritic cells, and lymphocytes to prevent infection and aid in the healing process. This process also consumes and competes for vitamin D3 and its metabolites. Several studies have found that serum 25(OH)D can drop by as much as 40% to 74% following knee surgery. This drop in 25(OH)D was associated with an increase in serum pro-inflammatory cytokine (i.e., TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , GM-CSF, and IL-6) concentrations [5, 6]. One CHer reported falling out of remission while taking the anti-inflammatory regimen at a maintenance dose of 10,000 IU/day vitamin D3 following a broken bone and restorative surgery. The CHer reported he took 50,000 IU/day of vitamin D3 for five days and was back CH pain free by the second day.

**Beneficial Side Effects.** One of the more beneficial and immediate side effects of the anti-inflammatory regimen with respect to a favorable CH preventative response is an improved quality of sleep. Encourage CH patients to get at least 8 hours of uninterrupted sleep if at all possible. Quality sleep is an essential part of this regimen as it aids in the healing process.

Dr. Stasha Gominak, M.D., a neurologist in Tyler, TX, treats patients with sleep, chronic pain and headache disorders with a similar vitamin D3 regimen. She is also firmly convinced that sleep is an essential part of the healing process with these disorders. “Sleeping is not simply lying down and becoming unconscious. There are specific phases of sleep that we must achieve in order to repair and recharge brain cells. Without nightly repair and regeneration of the chemicals we need to feel good, the head pain system can be “on” every morning when we wake up. The daily preventative medications attempt to duplicate the chemicals we are lacking, and we can use them to make the headaches better, but the best fix of all is to improve the sleep so we make our own chemicals. Most people who have sleep disorders have vitamin D and secondary B vitamin deficiencies that cause their sleep to be interrupted or not restorative, i.e., they sleep, but still feel tired. Patients with vitamin D and B deficiencies often have body pain in addition to daily headache.” The VitaminDWiki website lists 80 health problems either prevented or treated with vitamin D3, most with evidence from an RCTs as proof. See the following link: <http://www.vitamindwiki.com/Proof+that+Vitamin+D+Works>

**About Vitamin D3 and Its Role in Cluster Headache, Neurogenic Inflammation and Pain.** The evolution of vitamin D3 related genetic sequences dates back over 500 million years to Cambrian period phytoplankton and zooplankton where these genetic sequences were responsible for mineralization of exoskeletons. There was a further major evolution of vitamin D3 related genes with the first vertebrates to metabolize vitamin D3 either from exposure to sunlight or from their diet, in order to develop and maintain a healthy mineralized skeleton. Yet another major evolution of vitamin D3 occurred with the first mammals, where its genetically active form began controlling other hormonal and genetic expression processes through vitamin D paracrine and autocrine functions. The human genome is populated with vitamin D3 related DNA sequences that reflect this evolution.

These encoded genetic sequences control not only vitamin D3 synthesis in the skin where the UV-B in sunlight strikes molecules of 7-Dehydrocholesterol turning it into vitamin D3 (cholecalciferol), but also its hydroxylation in the liver to 25(OH)D3 by the enzyme Vitamin D 25-hydroxylase also known as cytochrome P450 2R1 encoded in the human genome by the CYP2R1 gene. When needed as an endocrine function that maintains calcium homeostasis and builds bone mineral density, the kidneys further hydroxylate serum 25(OH)D3, with the enzyme 1 $\alpha$ -hydroxylase as encoded by the CYP27B1 gene to form 1,25(OH)2D3, the active vitamin D3 metabolite. By far, the most important and most numerous vitamin D3 genetic sequences control numerous other physiological functions through the extrarenal hydroxylation of vitamin D3 at the cellular and nuclear level throughout the periphery. It is these genetic sequences that enable the autocrine/paracrine signaling and genetic expression that are essential to healthy life.

A 2010 research study identified 2776 genomic positions occupied by the VDR and 229 genes with significant changes in expression in response to vitamin D3 [7]. Among these, one of the leading candidates and theory behind the mechanism of action by which vitamin D3 prevents CH deals with its capacity to down-regulate production of CGRP [8], specifically from neurons within the hypothalamus and trigeminal ganglia where concentrations of vitamin D receptors (VDR), 25-hydroxylase, 1 $\alpha$ -hydroxylase, and vitamin D binding protein (VDBP) are highest among brain structures [9]. Serum concentrations of CGRP have been found elevated during the pain phase of both cluster and migraine headaches [10, 11].

**About Omega-3 Fish Oil, the Vitamin D3 Cofactors, Vitamin B 50, Vitamin K2 and Vitamin C.** Omega-3 Fish Oil and the vitamin D3 cofactors are essential parts of the anti-inflammatory regimen. The vitamin D3 cofactors are not optional parts of this regimen as they play key roles in pharmacokinetics and pharmacodynamics of vitamin D3's capacity to prevent cluster headache.

- **Omega-3 Fish Oil** – The Omega-3 fatty acids DHA and EPA act with vitamin D<sub>3</sub> as natural anti-inflammatory agents. As vitamin D<sub>3</sub> is lipophilic, the Omega-3 fatty acids help increase vitamin D<sub>3</sub> absorption in the GI tract. Fatty acids are of paramount importance to all cells, since they provide energy, function as signaling molecules, and sustain structural integrity of cellular membranes. In the nervous system, where fatty acids are found in huge amounts, they participate in its development and maintenance throughout life. Growing evidence strongly indicates that fatty acids in their own right are also implicated in pathological conditions, including neurodegenerative diseases, mental disorders, stroke, and trauma [12].
- **Magnesium** – Magnesium is the single most important vitamin D<sub>3</sub> cofactor, as it is essential in the enzymatic processes that metabolize, (hydroxylate), vitamin D<sub>3</sub> to 25(OH)D<sub>3</sub>, (calcidiol) and 25(OH)D<sub>3</sub> to 1,25(OH)<sub>2</sub>D<sub>3</sub>, (calcitriol). As magnesium also supports the enzymatic processes that catabolize 25(OH)D<sub>3</sub> to inactive metabolites like 24,25(OH)<sub>2</sub>D<sub>3</sub> that are eliminated from the bloodstream by the liver in bile, it also helps lessen the likelihood of vitamin D<sub>3</sub> intoxication. Many physicians, research scientists and nutritionists now believe magnesium supplementation is more important than calcium in order to maintain healthy bones as well as a healthy heart. Magnesium helps keep calcium dissolved in the blood. Without the proper balance of magnesium to calcium, it's possible that calcium may accumulate in kidneys increasing the probability of kidney stones, rather than in bones where it's needed most. The more calcium taken without the balancing effect of magnesium, the more symptoms of magnesium deficiency and calcium excess people are liable to experience. CHers taking too little magnesium or none at all have reported symptoms including hand and leg cramps, muscle weakness and a few reported "heart flutter." These symptoms resolved rapidly when magnesium was increased to a dose of 400 to 600 mg/day.
- **Zinc** - An essential trace element and micronutrient, zinc is essential for the normal growth and reproduction. Zinc plays a key role during physiological growth, cellular division and as an antioxidant. Zinc supports immune functions and is vital for the functionality of more than 300 enzymes, for the stabilization of DNA, and genetic expression where "zinc fingers" have been found in Vitamin D Response Elements (VDRE) on target genes.
- **Boron** - An essential trace element and micronutrient, boron influences the metabolism of calcium, magnesium, phosphorous, and vitamin D. The need for boron is greatest during a vitamin D deficiency. Dietary boron reduces the risk of inflammatory disease by serving as a suppressive signal that down-regulates enzymatic activities typically elevated during normal inflammatory process [13].
- **Vitamin A (retinol)** – Retinol plays a key role in vitamin D<sub>3</sub>'s autocrine and paracrine paths of metabolism that take place at the cellular and nuclear level. This is where the body converts retinol stored in the liver to one of the retinoic acids that combine with 1,25(OH)<sub>2</sub>D<sub>3</sub> to form a heterodimer that acts as a genetic bridge between a vitamin D<sub>3</sub> receptor (VDR) and Retinoic X Receptor (RXR) in a vitamin D<sub>3</sub> response element (VDRE). In this role, the vitamin A retinoids are essential in vitamin D<sub>3</sub>'s capacity to enable genetic expression.
- **Vitamin K2 (MK-4 and MK-7)** – The vitamin K2 menaquinones, MK-4 and MK-7, are not directly involved in vitamin D<sub>3</sub> metabolism. Where vitamin K2 comes into play occurs with the increased calcium kinetics made possible by the higher doses of vitamin D<sub>3</sub> and higher serum



concentrations of 25(OH)D needed to prevent CH. Daily intake of vitamin K2 complex is suggested as dietary supplements for healthy individuals to prevent loss of bone mineral density. In addition, a dietary menaquinone intake is associated with reduced coronary calcification. Adequate menaquinone intakes could therefore be important to prevent cardiovascular disease [14, 15]. For patients on oral anticoagulant treatment, careful addition of vitamin K2 appears to offer protection against coumarin-induced side effects and to reduce diet-induced fluctuations in their INR values. A cardiology consult is essential before starting oral vitamin K2 in patients with mechanical heart valves. The preferred menaquinone is MK-7. It has a half-life measured in days where MK-4's half-life is only a few hours.

- **Vitamin B 50 Complex**– A 3-month course of vitamin B 50 Complex helps address any of the B vitamin deficiencies and in the process, helps reestablish friendly colonies of flora “microbiome” in the GI tract. This in turn enables the production of many B vitamins and a healthy immune system. Clinical evidence collected by Dr. Stasha Gominak, MD suggests Vitamin B12 and Folate may deplete without supplementation while taking vitamin D3 at physiological doses for two years or more. The Vitamin B 50 Complex is formulated with 50 mcg Vitamin B12 and 400 mcg Folate (Folic Acid).
- **Coenzyme Q10** - Although not a part of the anti-inflammatory regimen for CHers, migraineurs taking this regimen to prevent their migraine headaches have reported an improved response by adding CoQ10. It is also highly recommended when taking statins.
- **Curcumin** - Curcumin is naturally occurring phytochemical that modulates numerous molecular targets with antioxidant, anti-inflammatory, and neuroprotective activities. 500 to 1000 mg/day is an excellent pain reliever and natural alternative to taking NSAIDs (aspirin, Tylenol, ibuprofen, etc.) as all NSAIDs cause GI tract bleeds, even the “heart healthy: 81 mg aspirin.
- **Vitamin C** - Humans lack the genetic resources to synthesize vitamin C so must obtain it from dietary or supplemental sources. Vitamin C functions as an essential cofactor in numerous enzymatic reactions, e.g., in the biosynthesis of collagen, carnitine, and catecholamines, and as a potent antioxidant. Vitamin C also functions as a non-toxic antibiotic, antiviral, and antifungal agent at oral doses from 2 up to 8 grams/day taken at 1000 mg every two hours.

With the exception of Omega-3 Fish Oil, a natural anti-inflammatory, calcium and vitamin K2, which aid in building bone mineral density, the remaining supplements in this regimen are vitamin D3 cofactors that aid in vitamin D3 metabolism and its autocrine/paracrine signaling role in promoting genetic expression.

American Academy of Neurology published an abstract of survey results as of 20 April 2014 in their journal Neurology. You can find this abstract at the following link.

[http://www.neurology.org/content/82/10\\_Supplement/P1.256](http://www.neurology.org/content/82/10_Supplement/P1.256)

The poster presentation of survey results on 28 April 2014, at the AAN Annual Meeting in Philadelphia, PA was well received.

**Study Design and Strength of Medical Evidence (Class IV).** This was a participant funded, self-reported, open label, prospective cohort study with no blinding or placebo control group. Participants served as their own control group for the 25(OH)D response making the level of medical evidence at best Class III.

Data from this study confirm an inverse relationship between 25(OH)D serum concentrations and CH frequency. There are a number of factors that add strength to the study findings. With 187 survey participants and an estimated US population of 300,000 CHers, the statistical significance of the survey results is relatively high. In addition, CHers tend to be exceptionally compliant when it comes to following dosing instructions. With respect to a placebo control group, the raw efficacy of 53% for a sustained pain free end point response to the anti-inflammatory regimen is well beyond the highest reported placebo response in CH of 14% to 43%, the lowest value was reported using the strict endpoint; cessation of headache attacks [16].

**Acknowledgments.** I would like to thank the following people for their contributions to the online survey of CHers taking the anti-inflammatory regimen to prevent their CH and in the development of this suggested CH preventative treatment protocol:

**Paul Craig** – for setting up and running the online survey of cluster headache sufferers taking the anti-inflammatory regimen to prevent their cluster headaches since December of 2011.

**Dennis and Stephanie Johnson** - <http://www.clusterheadaches.com> for running and administering a world-class cluster headache forum and web portal dedicated to cluster headache sufferers and their supporters with over 11,000 members worldwide. Without this forum none of my research on the capacity of vitamin D3 to prevent cluster headache would have been possible.

**Carol Baggerly** - <http://www.grassrootshealth.net> Director GrassrootsHealth for providing access to the GrassrootsHealth D\*Action database of 10,200 25(OH)D lab tests taken every six months from 3657 individuals taking vitamin D3 from 0 IU/day up to 20,000 IU/day. 1600 of these lab tests were taken at a vitamin D3 dose of 10,000 IU/day.

**Henry Lahore** - <http://www.vitamindwiki.com> for conceiving and administering the most informative and “go to” websites covering all things vitamin D3 and the vitamin D3 cofactors.

**Dr. Peter Lewis, MD** – <http://www.yourhealth.com.au> An Integrative physician in Manley (NSW), Australia, for reviewing early survey results and pointing out the non-skeletal health benefits of vitamin D3 when taken at physiological doses of 5000 to 10,000 IU/day.

**Dr. Robert P. Heaney, MD** – <http://www.grassrootshealth.net> Professor Emeritus Creighton University School of Medicine and Research Director, GrassrootsHealth for answering my emails and taking my calls, then pointing me towards the extrarenal hydroxylation vitamin D3, autocrine/paracrine signaling and genetic expression as key factors in the mechanism of action underlying the capacity of vitamin D3 to prevent CH. We lost Dr. Heaney August 10, 2016. He was a giant in the field of endocrinology, bone, mineral and vitamin D research.

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