Background:

Currently there are no proven effective treatments for chronic fatigue syndrome (CFS).

Most experts strongly suspect that Herpes Class viruses such as Epstein Barr Virus (EBV), HHV-6, and/or Cytomegalovirus (CMV) play an important role for some but not all CFS patients.

Several leading CFS specialists offer selected patients the option of treating with Valtrex or Famvir, two anti-viral medicines. These are usually used to treat cold sores, which is caused by Herpes Simplex virus or Shingles, which is caused by the chicken pox virus. For some CFS specialists these are their first choice anti-virals. Others prefer Valcyte (valganciclovir), believing that Valcyte is more effective. However, Valcyte may be more prone to potentially serious side effects. Valcyte is also much more expensive.

Like Valcyte, neither Valtrex nor Famvir is approved by the FDA to treat Epstein-Barr Virus, HHV-6 or Chronic Fatigue Syndrome per se.)

Despite anecdotal support, there are no well controlled double blind studies testing the effectiveness of Valtrex or Famvir for CFS. Martin Lerner, M.D. has reported a large series of patients from his practice, who have done well with these medicines. Dr. Lerner’s publication can be downloaded from this address. http://www.dovepress.com/subset-directed-antiviral-treatment-of-142-herpesvirus-patients-with-c-peer-reviewed-article-VAAT

Please note that Dr. Lerner often uses doses of Valtrex or Famvir that is considerably higher than the dose recommended by the FDA for the treatment of shingles or cold sores. In contrast, I and several other CFS specialists tend to use lower doses to reduce the potential for side effects.
Most CFS specialists who use anti-virals tend to treat patients who have very high levels of antibodies against Herpes Class viruses such as Epstein-Barr virus or HHV-6. We believe that patients with very high antibody levels are more likely to have active infection. Unfortunately, standard lab tests cannot definitely distinguish between latent, inactive versus active recurring infection. Therefore, we cannot be certain which patients will respond to anti-viral treatments.

Until controlled studies are done, I prefer to offer Valtrex or Famvir because of their safety and cost advantages, However, I am willing to offer Valcyte for selected patients. Dr. Lerner tends to start with Valtrex rather than Famvir; but if Valtrex causes side effects such as diarrhea, he then switches to Famvir. Other physicians tend to start with Famvir.

**Eligibility for Valtrex or Famvir Treatment Protocol:**

- Must have chronic fatigue syndrome.
- Must have relatively high antibody levels to Epstein Barr Virus and/or HHV-6 virus.
- Must be between ages 21 and 60.
- Although both Valtrex and Famvir are rated as category B for pregnancy (relatively safe), our patients must agree not to become pregnant throughout the course of the treatment. Men should use barrier contraceptives during treatment and for at least 90 days after stopping treatment.
- Must have normal kidney function.
- Must understand that treatment with Valtrex or Famvir for chronic fatigue syndrome is an “off-label” treatment, not approved by the FDA. Although as medicines go, these drugs are “relatively” safe, potentially serious side effects can occur. Side effects are probably more common at higher doses.
Must have adequate home support available. Some patients with antivirals might tend to get worse before they get better.

The patient should understand that can take six months or longer to judge whether improvement is occurring.

Complying with laboratory and medical monitoring is critically important. There will be monthly blood and urine tests. There will also be monthly medical visits. Patients who are doing well might possibly be seen at longer intervals.

Patients must have the financial resources to maintain Valtrex or Famvir therapy for at least six months. Insurance will often cover treatment, but not always. If higher than usual doses are used, insurance coverage will more often be a problem.

Before starting Valtrex or Famvir the patients and supervising clinicians should read the FDA approved Package Insert document. These are available on line.

For Valtrex:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020487s014lbl.pdf

For Famvir:
http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c5617ff1-33a1-4d50-9b1c-e3fc4767f373

The following is a brief and only partial summary of information from the drug package insert for Famvir(famciclovir) and Valtrex (valacyclovir) Patients should ask the physician any and all questions that may arise at any time before or during their treatment.

**FDA Approved Indications:** Both medicines are FDA approved to treat cold sores, genital herpes and shingles. Cold sores and genital
herpes are typically due to Herpes Simplex virus. Shingles is due to a reactivation of Varicella (chicken pox) virus.

**WARNINGS and Precautions:** Both Famvir and Valtrex can cause acute renal/kidney failure when taken at higher than recommended doses, and in the elderly. The risk is probably greater if kidney function is already impaired; but renal failure can also occur among persons with previously normal kidney function.

Among patients with advanced HIV disease and also among patients with kidney transplants or bone marrow transplants high dose Valtrex (8 grams) a day was associated with a dangerous blood clotting and bleeding syndrome called Thrombotic Thromocytopenia Purpura/Hemolytic Uremic Syndrome.

Among elderly patients given very high doses of Valtrex agitation, hallucinations, confusion, delirium, seizures and encephalopathy have been reported.

**Comment:** For our protocol we will treat only persons with normal kidney function. We will check kidney lab tests frequently.

**Side effects:** The most common side effect (>10%) are headache and nausea. Other side effect effects include nausea, diarrhea

**Possible “die-off” reactions:** When treatment is started there is sometimes a flare up of symptoms. This might be due to the breakdown of viral particles, a so-called “die-off” reaction. However, it can at times be difficult to distinguish a “die-off” from an allergy to the treating medicine. If your symptoms increase when you start treatment, either rapidly or slowly, promptly notify your doctor.

**Both medicines may be taken with or without food.** If there GI symptoms occur, the medicines might be better tolerated if taken with food.
**Drug Interactions:** Known adverse interactions are few. However, be sure that your pharmacist checks the drug interaction function of the pharmacy computer for potential interactions whenever you add or change medicines.

**Pregnancy:** Both Famvir and Valtrex are Category B for pregnancy. This means that no adverse effects have been reported in women or in animal studies. However, our protocol will require that both women and men maintain contraception during the time they are on treatment.

For **Famvir** female rats treated with high dose Famiclovir for two years had an increase in breast cancer rates. (The rat strain studied normally has a high incidence of breast cancer). Female mice and male rats and mice showed no increase in cancer. **Valtrex was not-carcinogenic** in mice treated throughout their lives with relatively high doses of Valtrex.

For **Famvir Testicular atrophy** was observed in male rats, mice and dogs. Two placebo-controlled studies in 130 otherwise healthy men treated with Famvir for 18 weeks showed no significant adverse effects on sperm counts. Special note: Famvir tablets contain a small amount of lactose. This might cause diarrhea among persons with severe lactose intolerance. It would not normally be a problem for persons with mild or moderate lactose intolerance.

**FDA recommended dosing (so as to compare with the doses we might use in our protocol):**

*Famvir:* For chronic suppression of recurrent entail herpes: 250 mg twice daily

For Shingles: 500 mg three times daily for 7 days.

For recurring acute episodes of genital herpes: 1000 mg twice daily for one day.

*Valtrex:* For Chronic suppression of recurrent genital herpes 1 gram (1000mg) daily

For shingles 3 grams daily for 7 day

For recurring acute episodes of genital herpes: 500 mg three times a day for 3 days
Treatment Protocol for Selected CFS Patients:

Step I: Medical Evaluation to assure that the diagnosis of chronic fatigue syndrome is satisfied, and that there are no contraindicating co-existing health problems. Pre-treatment lab tests include CBC, CMP, urinalysis; Epstein Barr Virus, HHV-6 and CMV anti-body levels. Other tests would be as medically indicated. In some cases we will require a 24 hour urine and blood test for creatinine clearance.

Step II: If using Valtrex, start at 500 mg for one to three weeks. If tolerated go to 500 mg twice daily or 1000 mg once daily for one or two months.

After 1 or 2 months we might or might not subsequently increase the doses in steps toward 1 gram twice daily. This is higher than the FDA recommended dose. Please note that a few chronic fatigue syndrome specialists use between 4 grams and 8 grams of Valtrex daily when treating CFS. We should assume that the risk of significant side effects increases as the treatment dose rises.

If using Famvir start at 250 mg once daily for one to three weeks, then go to 250 mg twice daily. After one or two months we may increase in steps to 500 mg twice daily, or in selected cases, somewhat higher.

Step III: CBC, CMP and urinalysis are required monthly. Epstein Barr, HHV-6 or CMV antibody levels will be tested at intervals.