

NIMODIPINE use in M.E. / CFS: A comprehensive guide.

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“...I believe effective medication can dramatically improve the health of a person with CFS for the better and change general practitioners' perceptions of the patient as improvements occur. Everyone feels more positive. Something can be done now.” Dr. Marilyn McNeill. (Notes: 80.)

“It is vitally important for the physician to be the patient's advocate. In the absence of any proven treatments, empiric therapies [as knowledgeable experiments] should be tried. At the same time, patients need to be kept from using exotic, untested remedies that may hurt them.” US Department of Health and Human Services. (Notes: 28.)

Please do not take any prescription drug without the express permission and guidance of a qualified medical doctor.

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I. PURPOSE of this PAPER

This report is a summary of the medical uses of nimodipine and a candid report of my survey into its use as a treatment for Myalgic Encephalomyelitis, a type of Chronic Fatigue Syndrome (M.E./CFS). It is my hope that the accounts in this paper of the various doctors that prescribe nimodipine, and the increased health that has been achieved by M.E. patients, will encourage a greater number of doctors to make this low risk and clinically tested treatment available to their patients.

I was housebound for many years due to M.E. but quickly improved and am now 80% of well. I can go out every day, go shopping, organise and participate in volunteer work, walk six miles a day, drive a car, enjoy foreign holidays, and research and prepare information. This significant improvement in my functioning is due to my use of nimodipine (Nimotop).

Any feedback regarding this document, as well as personal accounts of nimodipine use, are welcomed and desired. I would like to make this paper as comprehensive as possible. Please contact me, Susan Parker, at 59 Quarry Lane, Northfield, Birmingham B31 2PZ, U.K. or you can send me an email via s.parker.messages@btinternet.com.

II. DESCRIPTION of the DRUG nimodipine

The type of drug: Nimodipine (nih MO dih peen or nye MO' dih peen) is a second generation L-type calcium channel blocker, also called a calcium antagonist, in the dihydropyridine class.

In general, L-type calcium channel blockers (CCBs) slow the movement of calcium ions into the muscle cell membranes of the arteries throughout the body. The resulting lower

level of calcium in the blood vessel walls relaxes and widens them which improves the blood flow and energy into cells. They do not harm the strength of the bones.

CCBs which *act on the heart muscle* make it easier for the heart to pump and lower blood pressure and treat angina. These L-type *non-dihydropyridine* drugs include verapamil, gallopamil and fendiline.

CCBs in the *dihydropyridine* (DHP) class work more *on the blood vessels throughout the body* than on the heart, such as clinidipine used to lower blood pressure.

Only some of the DHP class drugs *cross the blood-brain barrier (BBB) and enter the cerebrospinal fluid*. These are amlodipine, azelnidipine, clevidipine, diproteverine, felodipine, isradipine, nicardipine, nifedipine, nilvadipine, *nimodipine* and Smith Kline drug number 9512 with the most potent being isradipine. (Notes: 19, 38, 71, 93, 97, 101, 110.)

Unique effects of nimodipine: *Nimodipine is the only calcium channel blocker to have a greater effect on arteries in the brain than elsewhere in the body*, so it is unlikely to affect blood pressure. Nimodipine's potent effect increases blood flow to all areas of the brain and the brainstem. This benefit reduces brain damage after a stroke or brain aneurysm, the drug's main use.

Nimodipine *crosses the blood-brain barrier into the central nervous system more easily than other DHP drugs. It is rapidly spread throughout the body to tissues and organs*. The drug also affects N-type and P/Q-type calcium channels which are in nerve tissue in the body and brain, so it can help to relieve chronic pain throughout the body. (Notes: 10, 36, 38, 51, 55, 96, 113.)

Nimodipine increases the healthy functioning of the entire body. It has been shown to hamper the effect of viruses and toxins formed by disease as well as common environmental pollutants, such as halogenated aromatic hydrocarbons. It has been found to be of benefit in many complaints, some of which are noted in Appendix 2. (Notes: 63, 70, 71, 91, 95, 113.)

Absorption: The drug is metabolized in the liver and absorbed by the intestines. Peak concentrations in the body are 30 to 60 minutes after taking the drug and it has disappeared from the body in five to ten hours. Tests have shown a progressive increase in blood flow from day 1 to day 5 of a trial when the amount of the drug found in the blood serum remained constant. The amount of the drug found in the blood serum varies widely between individuals with younger persons absorbing much less than the elderly, on average. Tests show that the blood flow increases as the dosage is increased. (Notes: 10, 13, 82.)

Side effects, safety and efficacy: This is considered a low risk drug with side effects occurring in very few patients. Trials have found that 4 in 100 patients had side effects, yet *more patients had side effects from the placebos than from the drug*. Side effects were rarely severe and, except in one case which may not have been caused by the drug, disappeared when the dosage was reduced or discontinued. Fewer side effects are seen at 120mg per day than at lower dosages. There are no signs of accumulation of the drug in the patient, and there are no indications of toxicity or liver injury, dependence, increased risk of cancer or gastrointestinal bleeding. (Notes: 10, 38A, 93, 96, 99, 104.)

Regarding long term safety and efficacy, the longest controlled patient study was 120mg of nimodipine daily for a length of 7 years. However, this was not continuous use as it was only taken at the start of cluster headaches. In some cases the treatment became less effective in the later years of the trial. This is a contrast to a dementia trial which found that the improvement is greater with longer treatment. Both trials found that *in some* patients benefits were lasting and *in others* the benefits did not last when treatment stopped. (Notes: 34, 73.)

There is an anecdotal reference of continuous use for 12 years by a stroke patient who has seen continual improvement. I have had nearly continuous use for 7 years, taking a maximum of 90mg per day with improving benefit over time. (Notes: 38.)

The longest controlled use of higher doses that I have seen was of 180 mg daily on a 6 month trial that gave benefit to patients with dementia, and 300 mg daily on a 16 week trial that gave benefit to HIV patients. (Notes: 63, 73.)

III. Relevant M.E./CFS PHYSIOLOGY

Many physiological systems of the ME/CFS patient have abnormalities. Some of these problem areas are the type of dysfunction that nimodipine moderates.

Brain matter and blood flow: MRI scans have found that mid-brain white matter volume decreases with fatigue duration in CFS patients. The researcher argues that this and other irregularities could arise from a dysfunction of the astrocyte cells. Astrocyte cells are needed for brain processing. (Notes: 7, 111.)

SPECT and CT brain scans have shown significant abnormalities to blood flow in certain parts of the brain in people with ME/CFS. Low cerebral blood flow is further reduced after active exercise (when it normally would increase). (Notes: 21, 57, 90, 116, 119, 126, 139.)

Dr. Jay A. Goldstein finds that Viagra (sildenafil citrate), which increases the amount of blood flow by dilating the blood vessels, reduces all symptoms in some CFS patients, however others have no success with it. One patient whom he treated for 10 years had not responded to any medication until she took Viagra whereupon she felt almost normal. Similar drugs are Cialis (tadalafil) and Levitra (vardenafil). (Notes: 45.)

A study of the use of 100 mg 3 times a day of Viagra in CFS has yet to report its findings. A study of 20 mg. Cialis every 3 days taken by 30 CFS patients for a total of 5 doses gave resulted in symptom reduction in 90% and pulmonary artery pressure improved in 84%. Both shortness of breath and fatigue after exercise improved. Separately, a CFS patient self-reports that 25 mg of Viagra acted quickly on the type of brain fog caused by headache in periodic use. (Notes: 52, 53, 123, 130.)

Cognitive functioning: A combined analysis of 50 studies of cognitive functioning in CFS showed problems with attention, memory and reaction time, especially notable when the patient required information processing speed and working memory over a length of time. "Brain fog" is often one of the most disabling symptoms of ME/CFS. (Notes: 29.)

Cerebral spinal fluid and spinal cord: Abnormalities in the spinal fluid and inflammation in the spinal cord indicate reduced blood flow from the brain and impaired sensory information travelling to the brain. (Notes: 23.)

Cell health: It is proposed that in M.E./CFS the key abnormality is dysfunctional ion channels (channelopathy) in the cell membranes. Studies have shown damaged mitochondria which give energy to the cells of the brain and muscles, fewer RNA in muscles and a defect in protein manufacture by the body in M.E. patients. (Notes: 23, 26, 37, 118.)

Five research groups have found a pattern of significantly increased oxidative stress which can cause cell damage in the muscles and brain of ME/CFS patients that relates to symptoms, symptom severity and exercise. (Notes: 114.)

Cardiovascular: In ME/CFS, the endothelium lining of the blood vessels, which controls the flow of blood, is damaged by free radicals. In addition, there is a permanent dilation of the large blood vessels forcing the small blood vessels to narrow, and a low circulating volume of red blood cells. Endocardiography tests show that pulmonary artery pressure does not drop in CFS patients during exercise as is necessary to increase blood flow to the heart.

Energy flow irregularities have been found in leg and heart muscle during exercise by CFS patients, which indicate that the muscle blood flow is abnormal. Other studies have found that the heart has a reduced ability to contract and it also takes much longer to relax; blood pressure is maintained at the cost of restrictive blood flow to the body.

These problems cause further complications in the lungs, give insufficient blood vol-

ume in the brain, and reduce the oxygen and nutrients distributed to the rest of the body. All systems are affected, including a reduction in the liver's ability to detoxify the body, therefore toxins accumulate. (Notes: 20, 23, 35, 56, 58, 62, 88, 94.)

Immune function: The immune-related protein RNase L is abnormal in CFS patients and is linked to their reduced exercise capacity. These results are consistent with a channelopathy involving oxidative stress and nitric oxide-related toxicity. (Notes: 112.)

In people with ME/CFS, natural killer cells are working deficiently and there is an enzyme on the white blood cells which is increased indicating that it is attacking disease. These findings indicate a possible role of infection in ME/CFS. (Notes: 39.)

IV. Doctors' PROTOCOLS for use of calcium channel blockers IN M.E

A few different CCBs have been used clinically or in controlled studies of M.E. patients. There have been successes with verapamil-SR, nifedipine and isradipine but it is generally thought that nimodipine's action on the brain will give the best result in M.E. Professional bodies and doctors of various disciplines are advocates of the use of these drugs, yet a few others advise caution. I have tried to state their advice as they would give it. A summary can be found in Table 1 at the end of Section IV.

The earliest trials and advice about nimodipine come from North America. Only the gel-filled 30 mg capsule was available, so the suggested starting dose was as low as possible, 30 mg. Many doctors today continue that practice, but better results might be obtained by a more gentle start now that the drug is available in a tablet which can be split.

A. Calcium channel blockers other than nimodipine or unspecified:

Dr. A. B. Adolphe (New Mexico) prescribed nifedipine: Dr. Adolphe practices in Albuquerque, New Mexico, U.S.A. He had an M.E. patient to whom he prescribed 10 mg nifedipine three times a day to treat the patient's migraine-like symptoms with headaches, numbness in his hands, and a complaint of his right arm turning purple. After five days his headache subsided and his family noticed a marked increase in his level of attention, mental organisation, memory retention and, most prominently, no excessive fatigueability. On several occasions, the patient has not taken the nifedipine, and within 72 hours the symptoms have returned. Continuing the medication seems to prevent the symptoms. (Notes: 2.)

Dr. N. Klimas and Dr. Robert H. Keller (Florida) prescribe verapamil: Drs. Klimas and Keller at the University of Miami School of Medicine and the Center for Special Immunology, both in Miami, Florida, U.S.A. They are highly regarded microbiologists and immunologists and have used verapamil to treat patients. Dr. Keller states that within one month of finding the optimum dosage, the drug significantly reduced fatigue, myalgia, and memory problems in M.E. patients with a corresponding decrease in immune system activation. (Notes: 63, 66, 132.)

Dr. Charles Lapp (North Carolina) prescribes calcium channel blockers: Dr. Lapp is a CFS researcher and clinician at the Hunter-Hopkins Center in Charlotte, North Carolina, U.S.A. He prescribes CCBs to relieve symptoms in CFS patients with headaches through an increase in cerebral blood flow. (Notes: 68.)

Dr. L.H. Lund-Oleson (Denmark) prescribed isradipine (Lomir): Dr. Lund-Oleson, Department of Radiology at Svendborg Hospital, prescribed a DHP CCB and improved the functioning of a CFS patient. The treatment began with a small amount of isradipine (Lomir) increasing after 2 days to 5 mg per day. The patient felt better after 5 days and improved dramatically during the following 5 weeks. After increasing the dosage to 7.5 mg per day the daily variability of her condition smoothed and she could live an active life, but not to the level of resuming her work as a doctor. Depression caused by her CFS was also lessened as a result of this treatment. After 10 weeks an attempt was made to discontinue the treatment but

all of the symptoms returned after 4 days. Treatment was resumed and all benefit was regained after 10 days. After taking the drug for 2 years, and 7.5 mg continuously for 18 months, no side effects were seen. It is supposed that the functioning was improved through increased circulation to cells previously damaged by a virus. (Notes: 76.)

Dr. Benjamin Natelson (New Jersey) prescribes verapamil: Dr. Natelson is the director of the CFS/FM Center associated with the University of Medicine and Dentistry in New Jersey, U.S.A. and is a professor of neurology. He prescribes CCBs, including verapamil, to treat headache and vascular instability symptoms in patients with CFS. (Notes: 64.)

Dr. John Walton (Oxford) studied verapamil: Dr. Walton was a professor of neurology at Oxford University, U.K. and very highly regarded. He has performed a study in which verapamil-SR was given for six months to 25 CFS patients. Immune system improvements were noted, as were enhanced memory, and reduced fatigue and muscle pain. (Notes: 117, 129, 134.)

W. F. Professional Associates (U.S.A.) reports on verapamil: W. F. Professional, a provider of pharmacy education in the U.S.A., reports that verapamil-SR is used to treat patients with M.E. and fibromyalgia, a related syndrome. It is thought that calcium channel blockers may increase the threshold of chronic pain receptors, thus reducing the number that fire throughout the night and interfere with sleep and immune function. A verapamil study has shown immune system improvements, enhanced memory, and reduced fatigue and muscle pain. The suggested dose is 60mg to 120mg at bedtime to avoid problems with drops in blood pressure and dizziness. (Notes: 129.)

Anonymous doctor advises a calcium channel blocker: *Clinician Reviews* has published advice on the management of CFS. When the patient faints due to vasodepressor syncope (lack of blood volume in the brain) it suggests that they are given a calcium channel blocker. (Notes: 127.)

B. Nimodipine, the quick response protocols: Some doctors expect the M.E. patient's response 4 to 6 hours following a dose to be indicative of the usefulness of nimodipine in their treatment.

Dr. Jay A. Goldstein (California) prescribed nimodipine: Dr. Goldstein, now retired, specialized in neuropharmacology and in the treatment of CFS/ME patients. He used nimodipine as a primary treatment for M.E. About 40% of his CFS/FM patients taking nimodipine experience relaxation, increased energy, decrease in tender point sensitivity, improved exercise tolerance, and enhanced mental clarity. Nimodipine has been shown to release dopamine, serotonin, and acetylcholine. Some of his patients have been taking the drug for years. Although the effect on the blood vessels remains the same over time, sometimes a greater dosage is needed to retain the reduction in symptoms.

He recommends taking 30mg to 60mg 3 times a day. He often prescribes other drugs to be taken at the same time to bring complete functioning to the patients. (Notes: 44, personal communication with Dr. C. Shepherd in 2008 about his personal communication with Dr. Goldstein.)

Dr. Jeff A. Sherkey (Toronto) prescribes nimodipine: Dr. Sherkey is a family physician who has also suffered from CFS. He watched Dr. Goldstein's clinic of CFS and fibromyalgia patients for a week to further his knowledge of Dr. Goldstein's advice. Dr. Sherkey has prescribed nimodipine in combination with other drugs and has CFS patients that have remained symptom free for years.

One woman who was unable to work for 8 years because of severe fatigue, pain and cognitive dysfunction responded 30 minutes after she took a 30 mg capsule of nimodipine with about a 50% reduction of her cognitive dysfunction. For 2 weeks, she took 30 mg 3 times a day, and then increased the dose to 60 mg 3 times a day. This improved her cognitive

functioning to about 80% of normal but it did nothing for her other symptoms. She is continuing the nimodipine with other drugs to relieve her pain and fatigue which has allowed her to return to work. She has remained nearly symptom free on these medications for almost two years. (Notes: 122.)

Dr. Jacob Teitlebaum (Maryland) advocates nimodipine: Dr. Teitlebaum, an internist, is widely respected across the U.S.A. for his specialist treatment of CFS/M.E. patients. His understanding of Dr. Goldstein's protocol is 30 mg of nimodipine is to be taken 1 to 4 times a day. (Notes: 128.)

Dr. Ellen Wiebe (Vancouver) studied nimodipine: Dr. Wiebe, in family practice, used a double-blind system in a 36 day clinical trial of nimodipine on one CFS patient. The patient took 30 mg per day for 3 days of either the drug or a placebo. The patient kept a diary of her sleep quality, muscle pain, mental "fog" and fatigue. The results showed marked improvements at the end of each nimodipine series of days. She continues to take the drug and appears to be fully recovered; she has returned to work and is active in her leisure time. (Notes: 136.)

Dr. Paul Worthley (Kent) prescribes nimodipine: Dr. Worthley is a Senior Physician at the private Burrswood Hospital in Kent, U.K. with a particular interest in CFS. He has prescribed nimodipine for many years as a primary treatment for cognitive impairment as it is a low risk drug that will increase blood flow to the microcirculation of the brain. He would start the patient on 7.5 mg then increase it by small gradations, expecting a response within 4-6 hours if that dose was effective. Use is then maintained at this level, usually 45 mg taken 2 or 3 times a day, but it could be up to 60 mg taken 3 or 4 times a day. Most of his patients recover about 50% of their cognitive functioning but do not get any relief from their physical symptoms. He has not seen side effects from nimodipine. Dr. Worthley uses additional treatments to boost functioning over time. As there are different pathologies underlying the M.E. syndrome, a different set of treatments will be successful for each person. (Notes: 138, personal communications 2013, and personal communications with a patient 2013.)

C. Nimodipine, the slow response protocols: Some doctors allow 4 days to 2 months before concluding if nimodipine was useful in the treatment of M.E.

Drs. B. Carruthers; A. Kumar Jain; K. De Meirleir; D. Peterson; Nancy Klimas; M. Lerner; A. Bested; P. Flor-Henry; P. Joshi; P. Powles; Jeff Sherkey; and M. van de Sande advocate nimodipine: These doctors formed a working panel and produced *The Canadian ME/CFS Guidelines*. Their advice is that nimodipine is a useful treatment to improve mental clarity and it may also increase relaxation, reduce fatigue, decrease tender points, and improve exercise tolerance. It does not work in all ME/CFS patients. The suggestion is to start with 30 mg. and watch for low blood pressure. Then gradually increase to 60 mg twice a day if side effects are limited and tolerated. (Notes: 22.)

Dr. Paul Cheney (North Carolina) prescribes nimodipine: Dr. Cheney proposes that toxins have accumulated in the brain of a person with M.E. and lead to alterations in the normal firing pattern of neurons in the brain. This causes sustained arousal of the neurons and agitated exhaustion. Drugs that slow nervous system responsiveness will reduce nervous system symptoms. Nimodipine, nicardipine, nifedipine, and verapamil will all do this, but nimodipine is the most effective because it also addresses the problem of low blood flow to the brain. (Notes: 24.)

Dr. Tahir Majeed (Lancashire) prescribes nimodipine: Dr. Majeed is a Consultant Neurologist at Royal Preston Hospital and Royal Lancaster Infirmary, and in private practice in the U.K. He has been prescribing nimodipine since at least 2007. He uses nimodipine in patients with ME, starting with 30 mg and increasing it weekly by 30 mg per day to the total dose of 30 mg three times a day, provided there are no side effects. The usual side effects are

ankle swelling and flushing. Approximately 30% of patients partially respond to this treatment to alleviate their mental and physical fatigue. If they respond then they are advised to continue taking it and the others who do not respond, after 2 months they are advised to stop taking it. (Personal communications 2007, 2013.)

Dr. Helmut Roniger (London) prescribes nimodipine: Dr. Roniger is a Consultant at the Royal London Hospital for Integrated Medicine, central London, U.K. He sees many CFS patients and has prescribed nimodipine to myself and others, starting with a fraction of a 30 mg tablet and building up to a maximum of 90 mg per day to a useful level of improvement.

W. F. Professional Associates (U.S.A.) reports on nimodipine: W. F. Professional, a provider of pharmacy education in the U.S.A., reports that nimodipine is used to treat patients with M.E. and fibromyalgia, a related syndrome. It is thought that calcium channel blockers may increase the threshold of chronic pain receptors, thus reducing the number that fire throughout the night and interfere with sleep and immune function. Patients using nimodipine report decreased pain sensitivity, increased energy level, exercise tolerance and mental clarity. It acts primarily on cerebral arteries and has few side effects. The suggested dose of nimodipine is 30 mg daily. The patient should show improvements within four days. (Notes: 129.)

Dr. Rowan Wilson (Wales) is optimistic about nimodipine: Dr. Wilson is a Consultant Psychiatrist in Haverfordwest, Pembrokeshire, U.K. At the request of a patient with M.E., he has investigated the use of nimodipine and is willing to work with the patient's GP in prescribing the drug, starting at 30mg for a few weeks, then building up to 120 mg per day. (Notes: 137.)

Dr. Andrew Wright (Lancashire) prescribed nimodipine: Dr. Wright, now retired, was a private primary care doctor in the U.K. and one of the Medical Advisors to Action for ME. He has told me that he prescribed 90 to 120 mg per day of nimodipine to M.E. patients. (Notes: Personal communications 2007, personal communications with a patient.)

Anonymous: I know of a Professor of Vascular Medicine in Scotland, a Consultant Endocrinologist in Warwickshire, a Professor in Finland, and a CFS specialist in Belgium who have prescribed nimodipine to M.E. patients, and a Consultant Rheumatologist in London who would consider prescribing nimodipine.

C. Nimodipine, the slow toxin release protocols: The evaluation of the proper dosage is sometimes based on the side effects, which are to be expected as toxins are released from the body. This approach originated with Dr. Mason Brown.

Dr. David Mason Brown (Scotland) prescribed nimodipine: Dr. Mason Brown, a retired Scottish General Practitioner, has also suffered with CFS. He has treated M.E. patients for more than twenty years and about 80 per cent of them either recover completely or nearly so. It is said that he has restored a good quality of life to over 100 patients. Many M.E. Groups have his *M.E. Action Pack 1* in their lending library.

His programme has four components in an effort to fix the body's healing mechanisms which are malfunctioning. He uses nimodipine in the first step of treatment, along with a lot of filtered or bottled water to flush toxins from the body, ginkgo biloba, L-glutamine, evening primrose oil, and probiotics. The plan is to increase brain and total body circulation and functioning, and to improve nourishment of the cells. The pace of treatment is controlled by the patient, so when viruses and toxins that are being released and flu-like symptoms increase (which are necessary for the healing), the treatments can be moderated until the symptoms ease.

It is vital to begin at no more than 1/4 tablet (7.5 mg) per day. In the beginning take them with food because you want the process to be slow. Increase the dosage by 1/4 tablet

(7.5 mg) each week, possibly up to four tablets per day, split between morning and afternoon. For those that are severely ill, a smaller amount taken every third day is advised. It is important to drink 8 glasses of water each day.

When headache, flushing, nausea or rapid heartbeat is brought on by a new dose, continue another week at the old dose before trying the increase again. If the symptoms re-occur then the old dose is your maximum effective dose. Continue at that dose until you again get symptoms, then gradually reduce the dosage by 1/4 tablet each time you have them. Most patients find that after a time they will stabilize on a low daily amount, such as 1/2 tablet or 15 mg for 3 to 5 months, then it should only be needed on exceptional days. Take up to 120 mg if extreme activity is anticipated. (Notes: 25, 37, 41, 77, 78.)

Dr. Kristina Downing-Orr (London) prescribes nimodipine: Dr. Downing-Orr, a Clinical Psychiatrist and alternative practitioner, has been extremely debilitated by CFS. She has followed Dr. Mason Brown's programme and has regained great energy and health. She promotes his method in her book, *Beating Chronic Fatigue*. (Notes: 37.)

Dr. M. McNeill (Scotland) recovered through nimodipine: Dr. McNeill, a Scottish doctor now retired, was in hospital for a year and bedbound for a total three years due to M.E. symptoms of severe postural hypotension and low intracranial blood pressure. She followed Dr. Mason Brown's protocol on the use of nimodipine, and also used complementary treatments.

She didn't see any improvement until the fifth day of taking nimodipine. On that day she felt an "upswell" of energy and began to feel much better. Her mental activity improved to such a point that she was able to return to professional activity. She cautions that activity should be increased gradually and limit expectations as it is very easy to do too much and get a relapse.

Her general practitioner was so impressed with her recovery that he began prescribing her nimodipine on an NHS prescription (which could be filled at a low cost to the patient). She wanted to tell others about her recovery and she has written letters to medical journals and patient support journals. I have gained further knowledge through our personal communications.

Regarding dosage, she never took more than one and a quarter tablets daily (37.5 mg) and the total course was less than two months. She suggests limiting long-term use to one tablet in the morning, or the lowest dose that gives the patient's brain a boost, although at some point it should be tapered down to see if it is still needed. Additional low doses can be taken on an as-needed basis if a requirement for extra effort is anticipated. (Notes: 79, 81, personal communications.)

D. Caution advised in the use of calcium channel blockers:

Dr. Abhijit Chaudhuri (Scotland) studied nimodipine: When Dr. Chaudhuri was practicing at Southern General Hospital in Glasgow, U.K., he and Professor Peter Behan, on the basis that calcium channel abnormalities appear to be particularly associated with fatigue, studied the use of nimodipine by ME patients. They began with 1/2 tablet (15 mg) per day and many of the people got low blood pressure. Despite finding that the drug was partially effective in relieving muscle pain he said, in conversation with my general practitioner in 2007, that he would not use the drug again on M.E. patients because of the hypotension concerns. (Notes: 27.)

Dr. Charles Shepherd (U.K.) cautions about use of nimodipine: Dr. Shepherd of the U.K.'s M.E. Association at one time suggested a patient try the CCBs verapamil or nimodipine if muscle pain and mental functioning does not respond to other treatment, but now he emphasizes caution due to the drugs' lack of safety trials on M.E. patients and uncertainty of benefit. (Notes: 118, 120, personal communications 2008.)

Table 1. SUMMARY OF CALCIUM CHANNEL BLOCKERS PROTOCOLS FOR M.E.

Other CCB Used	Treatment Protocol	Benefits Realized	Side Effects	Practitioners
Isradipine.	*Gradually to 7.5 mg per day. *Must continue it to retain benefits.	*Resumed active life. *CFS-caused depression reduced.	*None seen.	Dr. Lund-Oleson.
Nifedipine.	*10 mg 3 times a day. *Must continue it to retain benefits.	*Eliminated excessive fatigueability, headache, numbness, cognitive problems.	*None seen.	Dr. Adolphe.
Verapamil.	*60 mg to 120 mg at bedtime. *Continue for 6 months.	*Reduced cognitive and physical symptoms, headache, vascular instability. *Decreased immune system activation.	*Blood pressure reductions, dizziness.	Dr. Klimas, Dr. Keller, Dr. Walton, W.F. Prof.Assoc., Dr. Natelson.
Unspecified.	*Unspecified.	*Relieves headache. *Eliminates fainting.	*Unspecified.	Dr. Lapp, Anonymous.
Nimodipine Used	Treatment Protocol	Benefits Realized	Side Effects	Practitioners
Nimodipine (quick response protocols).	*Some start at 30 mg. If no benefit in 1 hour then discontinue. If benefit, increase by 30 mg to optimum benefit relief to max. 180 mg. *Some start at 7.5 mg. If no benefit in 4-6 hours , then increase dose until cut-off of 240 mg. If benefit is seen, then continue this dosage, usually 90 to 135 mg per day. *Often must be continued to retain benefits.	*Effective in 40% to 50% of patients. *50% to 100% improved mental clarity, relaxation and sleep quality, exercise tolerance, energy. *0% to 100% reduced physical fatigue, tender point and other pain sensitivity.	*Often none are seen. *(Rare) ankle swelling, flushing, low blood pressure, felt worse. *Continue nimodipine if side effects are limited and tolerated or controlled by additional medication.	Dr. Goldstein, Dr. Sherkey, Dr. Teitlebaum, W.F. Prof.Assoc., Dr. Wiebe, Dr. Worthy.
Nimodipine (slow response protocols).	*Start at 7.5 or 30 mg, increasing every 7 to 14 days. Maximum varies from 30, 90, 120 or 180 mg per day. * Allow 4 days to 2 months trial before discontinuing. *When optimum benefit is seen, stay at that dose. *Often must be continued to retain benefits.	*Effective in 30% to 50% of patients. *50% to 100% overall improvement, mental and physical.	*Often none are seen, especially if begin at 7.5 mg. *(Rare) ankle swelling, flushing, low blood pressure. *Continue nimodipine if side effects are limited and tolerated.	The Canadian ME/CFS Guidelines, Dr. Cheney, <u>Dr. Chaudhuri</u> , Dr. Majeed, Dr. Roniger, W.F. Prof.Assoc., Dr. Wilson, Dr. Wright.

Nimodipine Used	Treatment Protocol	Benefits Realized	Side Effects	Practitioners
Nimodipine (slow toxin release protocols).	*Start at 7.5 mg increasing weekly to 120 mg per day. *Reduce a little when side effects persist. *Increase again until side effects persist. *Benefits seen on 5th day of new dose. *After reductions, will stabilize around 15 to 30 mg per day for 3 to 5 months, then only as needed day to day.	*Effective quickly in 20%, in 6 months in 20%, and over a period of time to varying degrees in all M.E. patients. *This will flush toxins from the body allowing greatly improved mental activity, physical energy, and health. *Do not increase activity precipitately.	*Side effects of headache, flushing, nausea or rapid heartbeat are evidence that the drug is being effective at flushing the toxins. *May have difficulty sleeping if taken after 4pm. *If feeling of over-excitement then reduce dosage.	Dr.MasonBrown, Dr. Downing-Orr, Dr. McNeill.

V. PERSONAL ACCOUNTS of nimodipine use in M.E.

Few M.E./CFS patients have a chance to trial nimodipine. Most doctors have never thought about its use as a treatment, some doctors don't want to prescribe an off-label drug, and many patients (especially in the U.S.A.) have found the drug costs prohibitive, but this may change now that generic nimodipine is available.

Summary: Including my own history, I have researched 29 first-hand and 9 second-hand accounts of people who have M.E. and have taken nimodipine. Their nimodipine use is charted in Table 2 at the end of Section V. Benefit was seen by 24 out of the 38. (Notes: 3, 4, 5, 6, 25, 37, 41, 47, 52, 53, 60, 61, 69, 83, 85, 92, 108, 109, 122, 133, 136, personal communications.)

The Sample: Of the 38 people researched, 17 were recruited through advertisements in M.E. patient support group publications in the U.K. and 14 were seen at internet CFS or symptom discussion forums. This selection method probably weighted the sample to those that did not get a significant benefit from their use of the drug. People who regained health would be likely to terminate membership to these groups and not hear of the request for participants. The remaining 7 were from medical journals or direct publications by the subjects' doctors.

There are 8 males and 28 females in the sample (and 2 are unidentified). The subjects received their treatment in Canada, Czech Republic, Finland, U.K., and U.S.A.

Health before nimodipine: At least 17 of the 34 people researched were housebound, if not bedbound, due to M.E. before they began their nimodipine trial.

The Dosage: Two started taking nimodipine with a single dose of 1.875 mg (1/16 tablet) per day, 2 others started with 3.75 mg (1/8 tablet), but many started with 7.5 mg (1/4 tablet) per day. Even at the lowest starting doses, sometimes the drug was not tolerated. One person started at an extremely high dosage. He took 120 mg per day for a week and was very uncomfortable with side effects and so terminated the trial.

There may be benefit in starting with a low dosage. One woman who started with 30 mg and quit due to strong headaches from it thinks, in hindsight, that she might have tolerated it if she had started with a lower dose. That was the case with another woman who, when starting on a higher dose, got a headache. She then took only 7.5 mg on the second day without side effects, and then successfully increased the dosage.

However, others that started with 15 mg or 30 mg tolerated the drug quite well. Of

those who tolerated the drug, most then increased the dosage in increments of 15 mg or 30 mg. The maximum dosage the individuals took ranged from 22.5 mg to 180 mg per day. The maximum dosage taken by 6 of the persons was determined by the level at which they reached side effects on the second increase trial, as advised by the Mason Brown protocol. Their maximums varied from 22.5 mg to 45 mg. Another person got a headache at 30 mg so returned to a maintenance dosage of 15 mg.

Others did not have lasting side effects so stopped incrementing at what they considered a reasonable dose to allow a sound trial and be a low health risk. It is possible that one woman who never increased the dosage beyond 30 mg might have achieved better health if she had used more. Another woman briefly tried 90 mg but didn't see any increase in benefit, so returned to 45 mg as a maintenance level. She might have been too hasty in her evaluation of the higher dosage.

One woman with CFS had high doses of nimodipine as hospital treatment for a brain haemorrhage. She had 60 mg every 4 hours on a 24 hour basis for 6 weeks. By the end of it she felt nearly 100% well but quickly regressed when the drug was halted. She has trialled it subsequently, but has not been allowed to take enough of the drug to give her any benefit.

Length of Trial: Of the people who did not tolerate their starting dose, 4 took the drug for a week or less, 1 trialled for 3 weeks, and 1 continued for 2 months. These were probably fair trials.

Of those that tolerated the drug but never saw any benefit, 2 persons took it for only 1 day. This was Dr. Goldstein's protocol: to give one 30 mg tablet and check the patient in an hour. Many of his patients did respond this quickly, but this wasn't a fair trial for everyone. My research includes a woman and a man who first saw benefit after they had slowly increased to 45 mg and 90 mg, respectively.

Many of the others who never saw any benefit I don't have data on the length of their trial, but I know that 2 took it for 6 months and 1 took it for 7 years. Those were reasonable trials.

Those that saw benefit from the drug had trials ranging from 6 weeks to over 8 years. One stopped because the benefit was too small. Others found that retained the benefits without continuing to take the drug. The man who stopped after 6 weeks may have seen further improvement if he had continued. Dr. Mason Brown advises, "Nimodipine helps twenty per cent [of ME/CFS patients] very quickly, another twenty per cent over six months, and all others to varying degrees over a period of time." (Notes: 108.)

Many of this study's subjects are continuing to take nimodipine: 3 are still increasing the dosage, and 9 are on a maintenance dosage.

The Side Effects: The people who were not tolerating the drug at their starting dose reported headache most frequently. Other symptoms, each reported once, were an "icy" sensation in the head, vision problems, increased dizziness, delayed vomiting, and felt worse overall. The man who started at 120 mg had flatulence, swollen glands and possible interference with thyroid medication. The subject is not certain that these symptoms were a result of the trial. Swollen glands and thyroid problems have never before been mentioned in connection with this drug but perhaps they are due to the high starting dose. Everyone's symptoms settled after discontinuing the drug.

Of the people who tolerated and continued to take the drug, 12 of the 20 did not have any side effects. Two others had fleeting symptoms following a dosage increase. One had a bad headache for 24 hours only when increased to 15 mg, and she continued to increase to 60 mg without side effects. The other had mild nausea and a rush of foul-smelling-but-dry odour in the arm pits for a few hours on the 4th day following increases in dosage to 45 mg and 60 mg, and she continued to increase to 90 mg without side effects.

One woman had alterations to her menstrual cycle that may have been caused by ni-

modipine, but they resolved without a change in dosage. Minor symptoms of palpitations, cheeks warm and tingly, and headache were seen by 4 persons; these symptoms quickly stopped when they lowered the dosage. Following the Mason Brown protocol, they made a second attempt at the increased dosage and did not get a return of the symptoms, until they had reached the highest dose possible for them to take.

The Benefits: In this study there were 14 people that did not see benefit from the drug. The breakdown is: 8 persons that were intolerant to it, 3 persons who gave it a fair trial of 90 mg for 6 months or longer, 2 persons who took it only once, and 1 person of whom I don't have the dosage or length of trial data. These last three persons may have seen benefit if they had maintained a longer trial.

The remaining 24 of the 38 did see benefits from the drug, and increasing benefit as they raised the dosage. There is no correlation between maximum dosage and level of improvement. One man realized complete mental and physical health, apart from autonomic symptoms, from taking a maximum of 45 mg per day for 9 weeks in contrast to the 2 women took 90 mg per day for 6 months without any benefit.

In mental clarity and endurance, 11 people improved to 100% or 90%, 4 improved to 80% or 50%, and 7 improved 20% to 5%. Of those with the least improvement, 4 are continuing to increase the dosage so they may realize a greater benefit in time and, I suggest, 2 others might also benefit from an increased dosage as they are taking 30 mg and 60 mg without side effects.

Missing from the above is one man for whom the benefit was unspecified, and a woman who didn't see any improvement in mental functioning. Without knowing the dosage and length of time she had been taking the drug, I don't know if she might find advantage in stepping-up her trial. Her only benefit from nimodipine was a small but valuable reduction in crushing pressure on her skull when lying down. She tested this by stopping and restarting the drug.

Of the 22 persons in my study that are identified as having mental improvement, 16 also had improved physical functioning to nearly the same degree, and 1 other had improved general functioning but little physical strength. Usually, the first physical improvements were defined as improved great gains in strength and energy, with the symptoms of endurance limitations, muscle pain, and headaches taking longer to resolve. This finding is at odds with Dr. Worthley's experience; none of his patients had physical benefits.

Reducing the medication: Of the 24 persons who saw benefits from nimodipine, 8 were able to retain the benefits after reducing the dose and then stopping the medication. These men and women had varying degrees of improvement. Another woman retained the benefits after reduction but could not stop the drug completely, sometimes taking 30mg a day.

Three others saw benefit at daily use of 45 mg, 90 mg, and 360 mg (the latter was given hospital treatment for a brain haemorrhage) but could not reduce the dosage without a fall off in mental and physical functioning. One of these continues to take the drug. The other took it until her death of a perforated ulcer, which has not been connected to her nimodipine use.

Of the remaining 12 persons, some of them are still in the early trial stages and others have not given these details.

Conclusions: As the M.E. syndrome is variable in its initiation and course, so is the effect of nimodipine upon these people. This small study shows that the drug has the potential to help more than 60% of M.E. patients gain a small or fulsome improvement in their health. There does not appear to be any continuing health risks in a trial beginning with 7.5 mg per day and gradually increasing to 120 mg per day.

There could appear to be evidence here to support the Mason Brown theory that im-

proved health will be achieved by toxin release evidenced by side effects when taking nimodipine. However, some of those that saw benefit and some of those who retained benefit after cessation did not have these side effects, so the drug action in the body seems much broader than this one idea.

As evidence that nimodipine works differently to the CCB nifedipine, before her nimodipine trial, one woman had successfully been taking 60mg of nifedipine once a day to control Reynaud’s Syndrome symptoms; the nifedipine did not relieve her M.E. When she started taking nimodipine she had to stop taking the nefedipine. The Raynaud's Syndrome symptoms returned but she had a reduction in her M.E. symptoms, and she preferred that outcome.

Table 2. PERSONAL ACCOUNTS OF NIMODIPINE USE IN M.E. August 2013

Persons who did not receive benefit from nimodipine use, in order of dosage.

ID.	M/F	Daily Dosage	Continues to take it?	Benefits	Side Effects while using it.
TFG9	F	Unknown dosage. Took it for a few days.	No.	None.	Intolerant to the drug, as with all other medications.
PHX8	F	Unknown dosage. Unknown trial length.	No.	None.	Felt worse.
PHX2	M	Unknown dosage. Unknown trial length.	No.	None.	None.
TFGB	F	Unknown dosage. Took it for 6 months.	No.	None.	None.
LWC3	F	3.75 mg. Took it 2 days.	No.	None.	Weak legs, sleepy, dizzy, more severe headache than usual.
TFG6	F	1 st trial: 7.5 mg, for 1 week. 2 nd trial: 1.875 mg for 1 week with same results.	No.	None.	Worsening of existing vision problems, head pain and "icy" sensation in head.
LWC1	?	7.5 mg, reduced to 3.75 mg, for 3 weeks.	No.	None.	7.5 mg caused delayed vomiting. 3.75 tolerated for 3 weeks then delayed vomiting. Nausea, facial flushing, grogginess, increased incidents of M.E. crashing.
TFG4	F	7.5 mg for 2 months.	No.	None.	Splitting headache.
LWC2	F	30 mg, for 1 day.	No.	None.	None.
PRO3	?	30 mg for 1 day.	No.	None.	None.
AME3	F	30 mg. For 4 days. In hindsight, it was probably too high of a starting dose.	No.	None.	Strong headache.
TFG3	F	Unknown starting dose. 90 mg for 6 months.	No.	None.	None.
TFGA	F	Unknown starting dose. 90 mg for 7 years, twice tapering off and back up.	No.	None.	None.
TFG1	M	120 mg for 1 week.	No.	None.	Maybe interfered with thyroid meds. Flatulence, swollen glands.

Persons who did receive benefit from nimodipine use, in order of maximum dosage.

ID.	M/F	Daily Dosage	Continues to take it?	Benefits	Side Effects while using it.
BMJ1	M	Unknown.	Was planning to.	Benefit.	None given.
PHX5	F	Unknown dosage. Unknown how long has been taking it.	Was planning to.	Small reduction in skull crushing pressure when lying down.	None.

ID.	M/F	Daily Dosage	Continues to take it?	Benefits	Side Effects while using it.
BMJ1	M	Unknown.	Was planning to.	Benefit.	None given.
PHX5	F	Unknown dosage. Unknown how long has been taking it.	Was planning to.	Small reduction in skull crushing pressure when lying down.	None.
PHX3	F	Started with 7.5 mg 2 times a day. Trial is now in the 4 th day.	Was planning to increase dosage.	Small windows of mental clarity and physical energy.	None.
MEA2	F	Unknown. Took it at least one year.	Was planning to.	Improved energy, mental clarity. 70%.	None.
TFG7	F	Over a year from 1.875 to 7.5 mg. Then 22.5 mg for 2 months. Then 7.5 mg per week for 10 months. Total of 2 yrs.	No. Has retained the benefit.	Increased energy, improved overall functioning up to 50% of well.	Palpitations, flushing when needed to decrease dose.
FUS1	F	Unknown starting dose. 30 mg tried, reduced to 15 mg for 6 months.	No. Has retained the benefit since 2008.	Greatly improved cognition to 90% and general well-being. Reduced mental fatigue.	Headache at 30 mg.
PBM1	M	Started 30 mg and continued.	Was planning to.	Read, understand, retain information to 100%. Back to work.	None given.
TFG5	F	Unknown starting dose. Maximum of 30 mg, for 3 years,	No. Has retained the benefit.	Some 10% - 20% improvement to mental clarity.	None.
PRO1	F	1 st trial started too high a dose. 2 nd trial started 7.5 mg or less. Felt benefit at 22.5 mg.	Was planning to increase dosage.	Improvement seen.	1 st trial: Head-ache when started too high. 2 nd trial: None.
KDO3	F	Started 7.5 mg, only needed a small dosage as mental symptoms hadn't been too bad.	No. Has retained the benefit.	100% mental clarity. No physical change.	Light symptoms when needed to decrease dose.
KDO1	F	Started 7.5 mg. Unknown further dosages or when saw improvement.	No. Has retained the benefit.	100% mentally and physically.	Light symptoms when needed to decrease dose.
KDO2	F	Started 7.5 mg and increased. Had ME-caused depression. After a couple of weeks began improving. Unknown maximum.	No. Has retained the benefit.	100% mentally and emotionally, and physically which wasn't much affected by the M.E.	Light symptoms when needed to decrease dose.
WBE1	F	Started 30 mg for 3 days. Improvement seen by 3 rd day. Unknown maximum.	Was planning to.	100% mentally and physically.	None given.
AME1	F	Unknown starting dose. Maximum 37.5 mg reducing to 15 mg over 8 year course.	No. Has retained the benefit.	100% mental clarity, better physically. Still uses wheelchair.	Headache when needed to decrease dose.
MEA1	F	7.5 mg starting dose. 37.5 mg, for 2 months. Then 30 mg or more if needed that day. Took it at least 6 years.	Unknown.	Improved mental functioning and general health to 90%. Relapses if over active.	Facial flushing, headache when dose increased but not on second try.
AME2	M	7.5 mg starting dose. Maximum of 45 mg, for 9 weeks.	No. Has retained the benefit.	100% relief of brain fog and fatigue. Only has autonomic symptoms now.	Cheeks warm and tingly with dose increase but not on second try.

ID.	M/F	Daily Dosage	Continues to take it?	Benefits	Side Effects while using it.
BMJ1	M	Unknown.	Was planning to.	Benefit.	None given.
PHX5	F	Unknown dosage. Unknown how long has been taking it.	Was planning to.	Small reduction in skull crushing pressure when lying down.	None.
TFGC	F	7.5 mg starting dose with immediate improvement. Gradual improvement as increased up to 60 mg for more than 4 years.	Yes. Has not tried a reduction.	Cognitive functioning to 10%. No other benefits.	On increase to 15 mg got a bad headache for 24 hours. Temporary alteration in menstrual cycle. Itching when combined with Tramadol.
TFG2	F	Starting dose 30 mg. Took 90 mg, briefly but saw no benefit above 45 mg. Took it 5 years until death.	Died of a perforated ulcer. (No connection to nimodipine has been made.)	50% Improved mental clarity and physical. Reduced headaches, improved sleep.	None
PHX6	M	Started 30 mg. Has just increased to 90 mg and seen his first benefits.	Was planning to.	Some difference. 10%.	None.
TFG8	F	15mg starting dose. First improvement at 45 mg. Taken for 7 years, the last 4 years at 90 mg. Gradual improvement over the years.	Yes. When tried to reduce it, always lost benefit.	Mental functioning to 90%. Energy, endurance, warmth, sleep, 80% of well.	On increases to 45 mg and 60 mg, got nausea and a rush of foul-smelling-but-dry odour in the arm pits on the 4 th day.
PRO2	M	Started 7.5 mg, increased to 60 mg by 7 th week with some improvement. Increased to 90 mg.	Yes, planning to increase to a maximum of 120 mg per day.	A little better. 10%	None
PHX4	M	Unknown starting dose. At 30 mg every 4 hours (around the clock?) for less than 6 weeks = 180 mg?	No. Didn't give enough benefit to bother with.	Some improvement. 5%	None.
SHE1	F	Starting dose 30 mg. gave immediate improvement. 180 mg for at least 2 years.	Was planning to.	80% Improved cognitive function. No other benefits.	None
PHX1	F	1 st trial: 6 wks. hospital treatment for a subarachnoid (brain) haemorrhage, given 60 mg every 4 hours around the clock = 360 mg daily. 2 nd trial: a fraction of the hospital dose gave no benefit.	No. Was not able to get the prescription for dosage that would bring benefit.	Nearly 100%.	None.

VI. MY M.E. HISTORY and USE of nimodipine

My previous health: My immune system problems became evident in 1983 when I developed Multiple Chemical Sensitivity. M.E. came on suddenly, in 1991 when I was 34 years of age, about 6 weeks following a heavy flu. I was housebound and so fatigued that I was sleeping most of the day and night, and suffering from a broad range of M.E. symptoms.

Other treatments that I tried: Medical tests and advice have pointed me to a variety of treatments that have reduced my symptoms. Magnesium sulphate injections halted my decline; high doses of evening primrose oil for three months eliminated the twitching and "burning" in my limbs; undertaking an elimination diet to discover foods to which I was intolerant and then avoiding them cut out the chills, dizziness, swollen glands, a lot of the brain

fog, the constant heavy fatigue, and the brain-too-busy-to-sleep nights. I subsequently felt bright in the mornings but was still quite fatigued by any activity and needed a nap in the afternoon.

As my DHEA barely registered on tests and the adrenal curve was abnormal, I took DHEA supplements for 2 years. This resolved my orthostatic intolerance (brief drop in blood pressure upon standing) and slightly increased my energy and stamina. A course of tropisetron (Navoban) gave me a boost in functioning (but the expense to benefit ratio was high so I didn't repeat it despite my doctor's encouragement). Seven years of dietary advice and supplements, homeopathic treatments, and enzyme potentiated desensitization (EPD, an allergy treatment) from the Royal London Hospital for Integrated Medicine improved my nutrition, fitness and resilience. (Notes: 14, 18, 31, 87, 89, 125.)

20% of well before nimodipine: Despite the improvements, I was largely house-bound, going out occasionally on foot for short distances or on longer outings in a wheelchair. I needed a long nap every afternoon and a day or more of rest after an outing. I had a lot of muscle pain after a morning of light household tasks. I was about 20 to 25% of well.

I have listed these previous therapies to show the degree of improvement that I had before I used nimodipine. If I had tried it earlier I would not have evidenced much success as the benefit would have been masked by my food intolerance symptoms. It is also possible that the earlier treatments put my body's systems in a state where it could benefit from the increased blood flow to the brain and its knock-on effects of nimodipine.

30% of well on 45 mg nimodipine: At this point in 2006 my doctor thought that due to my otherwise poor quality of life, I should be allowed to take the unknown risk of using an untested drug. After researching the drug, I began taking nimodipine. I started on 15 mg (1/2 tablet) and increased the dose by 15 mg every two weeks. I didn't have any side effects, tolerating it well although I have a history of intolerance to some types of drugs.

On the 4th day of taking 45 mg per day, I got a sudden rush of foul-smelling odour in my arm pits and felt nauseous. The 5th day was the beginning of my improvement. I was notably better and the previous day's symptoms had subsided. I no longer felt sleepy the whole of the night so stopped sleeping in the afternoon, but I did need an hour of rest in a chair. At this dosage I couldn't do more outside of the house, but I was more active inside the house. I was about 30% of well.

55% of well on 75 mg of nimodipine: After two weeks I increased the dose to 60 mg per day and again got the odour and nausea on the 4th day, and then improved on the 5th day. At this point I didn't need an afternoon rest, and I could walk further and go out for a whole day. My muscle soreness, joint stiffness, cold extremities, and brain limitations were reduced.

After a year at 60 mg, I increased the dosage to 75 mg per day split between morning, noon, and late afternoon. I could do much more at this level, having improved in strength and ability and I was slowly reconditioning my mind and body. I was very busy in the home and could go out most days to do a little shopping. I participated in volunteer and social activities and enjoyed long day trips and holidays overseas. I could walk 3 miles a day. With the use of pacing to vary activities throughout the day and across days, I was functioning at about 55% of well.

In the same month that I increased dosage to 75 mg I also began injections every six months of 300,000 units of Ergocalciferol Vitamin D which would have boosted the general health of my body.

80% to 90% of well on 90 mg of nimodipine: In 2008 I increased the dosage to my present level of 90 mg per day, taken as 30 mg three times a day. I saw a gradual increase in benefit such that I now organise and manage large projects and studies using intensive as well as repetitive mental and physical activity. I can now walk 6 miles a day, run and dance, and

drive a car at home and abroad. In 2010 I was 70% of well and now, in 2013, I am about 80% of well with mental clarity nearing 90%. Much reduced but still a problem is face pain from continuous concentration, and neck cramp causing vertigo and nausea from carrying an item of moderate weight.

Trials at reducing the dosage: I have tapered down my dosage of the drug 5 times, but saw a progressive regression with each 15 mg reduction. I lost all benefit when I reduced to a dosage below 45 mg (which is the level at which I first felt a benefit.) After each reduction trial I have tapered the dose back up to the starting level.

My present health: I have now been taking nimodipine for more than 7 years and have never had any side effects other than the fleeting ones on the 4th day following a dose increase. My blood pressure has always been the low-end-of-normal; it hasn't been changed by the nimodipine use and doesn't cause dizziness.

I have regular blood screenings and have two "abnormal" results. My serum ferritin has occasionally been high, but that pre-dated the nimodipine use. My liver ALT enzyme varies from 30 to 84 (reference range of 10 to 35) and this is possibly caused by the nimodipine (2% get this effect), but it is a transient effect common with many medications and does not mean that the liver is harmed; my normal blood counts confirm this. (Notes: 10, 13.)

I continue various homeopathic remedies, and have regular vitamin D injections because I don't tolerate oral supplements. Although many of my intolerances have disappeared over the years, I still need Creon digestive enzymes to digest meat and fish, and I am still intolerant to herbs, spices, flavourings, onions, citrus, eggs, beef, apples, peppers, mustard, and a few other things. I have every reason to think that I will continue to make progress.

VII. PROTOCOL and recommendations for the use of nimodipine in M.E.

A. My recommended protocol of this low risk drug:

Increase dosage if well tolerated.

If side effects, decrease to previous dose for a week, then try the increase again.

Average = 90 mg per day but wide variation in maintenance dosage is seen.

Maximum = 120 mg per day. There is an increased risk of transitory side effects above 90 mg per day.

Benefit may be seen early but trial should continue until 90 mg per day for 8 weeks. After benefit is seen, evaluate further increases after 8 weeks. If no increased benefit, then maintain the previous dosage.

Every year or two, lower the dosage for 8 weeks to see if still required.

If sensitive to medications or over age 65, then start with 3.75mg in the morning for 2 weeks, then begin the following protocol.

Week 1:	7.5 mg in the morning	= 7.5 mg per day.
Week 3:	7.5 mg twice a day	= 15 mg per day.
Week 5:	15 mg, 7.5 mg, and 7.5 mg in spread doses	= 30 mg per day.
Week 7:	30 mg, 7.5 mg, and 7.5 mg in spread doses	= 45 mg per day.
Week 9:	30 mg, 15 mg, and 15 mg in spread doses	= 60 mg per day.
Week 17:	30 mg, 30 mg, and 15 mg in spread doses	= 75 mg per day.
Week 25:	30 mg, 30 mg, and 30 mg in spread doses	= 90 mg per day.
Week 33:	45 mg, 45 mg, and 30 mg in spread doses	= 120 mg per day.

B. Other health considerations: If you are pregnant or breastfeeding, have epilepsy, kidney or liver problems, swelling in the brain, have ever had bleeding in the brain, or have had a heart attack within the last month then this drug is not advised. Caution is advised for those under age 18 or over age 65 as safety trials have not been done on this group. Caution

is advised if you have low blood pressure. While this drug is taken, it may interfere with the ability to father a child. (Notes: 10, 12, 38.)

Before you try nimodipine, be sure you are avoiding all foods to which you may have a candida problem or food intolerance, and have treated any adrenal (cortisol and DHEA) or thyroid insufficiencies. These are common problems in M.E. and their symptoms will probably mask any improvement you may receive from nimodipine.

C. Drug and natural remedy interactions: For an up-to-date list of drugs that should not be taken at the same time as nimodipine, please reference the Electronic Medicines Compendium (www.medicines.org.uk) or Drug Information Online (www.drugs.com).

Some of the drugs for the following conditions *might have interactions* with nimodipine: anticancer, antiviral, azole antifungal, SSRI antidepressants, epilepsy, heart condition treatments, high blood pressure treatments, hepatitis C, narcolepsy, seizures, erectile dysfunction, tuberculosis, low sodium levels or AIDS drugs. The following should not be used: macrolide antibiotics; theophylline used for breathing problems; lithium; birth control pills; anti-ulcer drug cimetidine; diuretics ("water pills"). One of my correspondents periodically used Tramadol for pain relief without problems, but when she used it at the same time as taking nimodipine she itched all over. The itching ceased when she stopped the Tramadol while continuing the nimodipine. Tramadol has been cited as one of many drugs taken with nimodipine when itching or rash has occurred. (Notes: 10, 12, 13, 33, 38, 38A, 84, 93, 99.)

I advise *caution* to those taking thyroid medication. Although a study has shown that there is no drug interaction or effect on the pituitary release of hormones, I have spoken to one person who may have had a change in the effect of their thyroid medication when they suddenly began using a high dosage of nimodipine. (Notes: 49.)

Drugs that *can* be taken with nimodipine are glibenclamide for diabetes, diazepam (Valium), digoxin, indometacin, ranitidine and warfarin. (Notes: 10, 86, 101.)

Natural remedies that *should not be used* at the same time as nimodipine are Ephedra (ma huang), yohimbin and St. John's wort.

Multi-vitamin supplements can reduce the effect of nimodipine or lower your blood pressure, so use them *cautiously*. (Notes: 10, 38, 106.)

D. How to take the drug: As this drug might make you feel dizzy, some doctors feel that the first time you take it should be about an hour before bed with a little food. If that didn't cause any dizziness, then begin taking it regularly in the morning. Swallow the tablets with a drink of water.

If you are sensitive to medications or over age 65, start your trial with 1/8 of a 30 mg tablet in the morning for two weeks. Otherwise you should be safe starting with 1/4 of a 30 mg tablet. Increase the dosage by 1/4 or 1/2 of a tablet every two weeks. Divide the total taken between two or three treatments about four hours apart and try to be consistent about the times that you take it. The maximum dosage should be four tablets (120 mg) a day in divided doses. (Notes: 10.)

Avoid eating grapefruit or drinking the juice while taking nimodipine because it will increase the blood levels of the drug for up to four days. You should get advice from your doctor before using salt substitutes containing potassium. Drink alcohol with caution as it may cause dizziness or drowsiness. If you take the drug with a meal it will slow the absorption a little but will not affect the overall amount absorbed. Crushing the tablets will reduce the amount absorbed. (Notes: 10, 11, 12, 102.)

E. Possible side effects: About 4 in 100 people taking the drug for any reason get side effects which will disappear when the drug is discontinued, or sometimes just by lowering the dose. Some M.E. doctors believe that the patient will benefit from the drug only if they have side effects, theorising that these are caused by toxins being driven out of the body.

However, my contacts and the protocol of other doctors suggest that for many people benefit is seen without any side effects.

Low blood pressure has been reported by a couple of prescribing doctors; they can give other drugs to counter this effect. Side effects which have been reported to me by M.E. patients are headache, flushing, dizziness, palpitations, intestinal disturbance, nausea and brief sweating with a strong odour. Other reported effects are a feeling of warmth, pounding in the chest due to a fast or slow heartbeat, itching, rash or red spots on the skin, vomiting, or swelling in your ankles. If you get any of these symptoms, tell your doctor. (Notes: 10, 38, 99.)

If the symptoms are fleeting then you may want to continue on your present dose and later increase it further. If the symptoms continue or are uncomfortable, then consider lowering your dose to the point it was before the symptoms started. After the side effects stop, you may want to try the troublesome dose again as the symptoms may not repeat, and you may get an increase in benefit from an increase in the dose.

F. Seeing benefit: After tapering up, a two month trial at 90mg per day, if tolerated at that level, is necessary before determining that the drug will not give any benefit. About half of the people that try nimodipine will get some level of benefit. It may begin a few days after each toxin-releasing dose, or it may not appear until you are taking 30mg to 60mg a day.

Benefits can be greater alertness, mental clarity, energy and stamina, and a reduction in fatigue, muscle pain, and headache. Your improvement may or may not increase the longer you take the drug. You may ebb and flow in your response to the drug, and the dosage may need to be reviewed from time to time.

During this time you should consider that your mind and body may be out of condition despite a feeling of wellness. The drug itself may give a feeling of elation which could drive away caution and lead to a relapse. It is best to increase activities very slowly and gently, and to avoid commitments or new responsibilities for the first year. It is still necessary to use pacing to fit within the mental and physical activity level envelope available to that person as they have not been cured of M.E., only reached a level of relief from symptoms.

G. How to lower the dosage or stop taking the drug: At some point you will want to reduce the dosage to eliminate side effects or to make sure that it is still necessary to take it for the benefit retention. It is important to slowly reduce the dosage in ½ tablet (15mg) increments each week or two. Do not suddenly discontinue the drug.

H. Monitoring your health: Please be aware that the safety of the long term continuous use of this drug has not been established. Blood pressure checks, blood counts, and kidney and liver function blood tests should be routinely performed. (The liver enzymes can be slightly raised by nimodipine; this is harmless.) (Notes: 10, 93, 104.)

VIII. THE PRESCRIBING and purchasing of nimodipine

A. Drug forms and availability: Nimodipine is available in over 60 countries worldwide. In some countries it is in 30mg tablet form and in others it is in 30 mg capsules filled with a gel. These forms are not significantly different in their rate and total absorption. However, for use in M.E. it is wise to start with a dose less than 30 mg and the tablet form makes this possible. (There is also a third form, a liquid called Nymalize, which is meant for feeding tubes.)

The original branded preparation, Bayer's Nimotop, is becoming hard to find. Most countries now have generic products with various trade names. Generic preparations have the same active ingredient but may differ in composition. Before they could be sold, in countries with drug controls, they were tested to be sure that their action was the same as the original Nimotop. (Notes: 38, 40, 98, 101.)

It is better to use the tablet form rather than the capsule form. The tablet can be split

for gradations in dosage. The Bayer Nimotop capsule gel contents include peppermint and polyethylene glycol 400 which some people with M.E. may not tolerate. (Notes: 38.)

B. Licensing and approval of the drug. In the U.K. and the U.S.A., nimodipine has only been "approved" or granted a product licence to be marketed for treatment following bleeding on the brain. Safe and effective use of 360 mg in divided doses per day for 21 days in those patients has been demonstrated to government agencies.

Doctors may sometimes prescribe a medicine for use outside the terms of its marketing authorization. This is called off-label prescribing.

C. Prescribing medicines off-label: Any U.K. doctor may prescribe a medicine off-label if thinks a medicine will be effective in treating your condition and the same result cannot be achieved by a drug licensed for that condition. Such use should be supported by appropriate evidence and the doctor should feel competent in using the medicine. The prescriber must consider his professional responsibility and potential liability. (Notes: 48.)

An NHS prescription can be written for an "off-label" use (so that the patient can get it at low cost), but it is more likely that the doctor will choose to write a "private" prescription. The doctor may charge a fee for writing a private prescription. After the doctor has seen that it gives benefit to the patient, the doctor might then choose to prescribe it on the NHS, but this decision is many faceted and should not be expected.

A private prescription can be printed or written in ink on any notepaper and include: The date; the doctor's name, type of practitioner (i.e. doctor), practice address, telephone number, GMC number, and signature; the patient's name, address, and date of birth; the drug name (nimodipine), strength and form (30 mg tablets), instructions (how many to take each day), and the quantity (in 100s).

D. Filling the prescription: Nimodipine tablets come in cards of 10 with 10 cards in a box, so it would be helpful if the doctor would write the prescription for a multiple of 100. Since nimodipine is not commonly prescribed, a pharmacist may not wish to fill a prescription only if it will leave them with a partial box. The pharmacist will ask you the condition for which you are taking it and ask you if you understand that it has not been tested for this use. He is likely to call the doctor for confirmation of the prescription. It will take a day or two for the drug supplies to reach the pharmacist.

If a private prescription has been written, you can ask any U.K. dispensing chemist to fill it but they may not want to. NHS exemptions from prescription charges and pre-payment certificates do not apply to private prescriptions, so the patient will have to pay for the drug. The pharmacy will also charge a dispensing fee; this will be a flat fee, so a prescription for a greater quantity will give a lower cost per tablet. Prices will vary, so call a few different pharmacies asking for a quote for the quantity on your prescription.

The drug can be purchased from shops or from domestic pharmacies selling over the internet. The internet suppliers will require a mailed, faxed or scanned copy of the prescription. The package will have to be signed-for when received. Allow a week for delivery.

You may find a foreign supplier of nimodipine which, including the shipping costs, will supply the drug at a discount. In most countries it is legal to import prescription medicines for your own personal use. (It is not legal in the U.S.A. and you may encounter difficulties, but it is allowed under the following procedure, since there is no effective treatment available in the U.S.A.) Most countries will accept a prescription from a doctor in another country. A copy of the prescription, or a letter from the patient's doctor, which includes the illness to be treated and the doctor's contact information must accompany the medicine for import controls. No more than a three-month supply is allowed. The medicines should be kept in their original packaging. If mailed, the contents of the package should be listed on the outside. There is no tax or duty owed, but they must be sent by Recorded Delivery or a similar service such that they are signed-for when received. (Notes: 40, 48, 59, 121.)

Some countries, such as Mexico, do not require a prescription to fill the order, but one is still required by the import controls of most receiving countries. In any case, I would not advise taking this drug without the oversight of a medical doctor.

Be cautious about the legitimacy of the internet business because some may sell medicines that don't meet quality standards or are out of date. The World Health Organization has determined that more than 80 percent of medicines are counterfeit in some countries. (Notes: 72.)

E. The cost of nimodipine: The approximate cost of filling a prescription of 30 mg tablets of nimodipine in 2013 was, per tablet:

Quantity 30	£1.00	€1.24	\$1.60 (USD, CAD, AUD)
Quantity 100	£0.50	€0.78	\$1.00 (USD, CAD, AUD).

There may be additional costs: the doctor may charge a fee for writing a private prescription, the pharmacist may charge a fee for dispensing a private prescription, and there may be shipping fees. (Notes: 105.)

Appendix 1.

DOCTORS WHO PRESCRIBE NIMODIPINE TO M.E. PATIENTS

These doctors have permitted me to make public their willingness to consider this treatment. I hold notes of other doctors of whom I can only relay information privately. August 2013

Canada

Dr. Bruce M. Carruthers, MD. 3657 West 16 Ave, Vancouver, BC V6R 3C3.
Telephone: 604-224-1515.

Dr. Jeff A. Sherkey MD, CCFP, General Practice Family Physician, 168 Annette Street, Toronto, Ontario MP6 1P4. Telephone: 416-767-6383. Fax: 416-767-4898.

United Kingdom

Dr. Kristina Downing-Orr, Clinical Psychologist. (Private patients) 76 Harley Street Clinic, London W1G 7HH. Telephone 020-7631-3276. www.76HarleyStreet.com. (Advice) "Beating Chronic Fatigue: Your Step-By-Step Guide to Complete Recovery", by Dr. Kristina Downing-Orr, Piatkus, 2010, ISBN 978-0-7499-4093-5.

Dr. Tahir Majeed, Consultant Neurologist. Location 1: (NHS patients) Royal Lancaster Infirmary, Lancaster. Location 2: (NHS patients) Royal Preston Hospital, Preston. Telephone 01772-716-565. Location 3: (Private patients) 11 Moor Park Avenue, Preston. Location 4: (Private patients) BMI Hospital, Lancaster.

Dr. Helmut Roniger, Consultant of Integrated Medicine. Location 1: (NHS patients) The Royal London Hospital for Integrated Medicine, 60 Great Ormond Street, London WC1N 3HR. Telephone 020-3448-8880. Location 2: (Private patients).

Dr. Rowan Wilson, Consultant Psychiatrist. (NHS patients) Canolfan Bro Cerwyn Centre, Fishguard Rd, Haverfordwest, Pembrokeshire SA61 2PG. Telephone 01437-772-827.

Dr. Paul Worthley, Senior Physician. (Private patients) Burrswood Hospital, Groombridge, Tunbridge Wells, Kent TN3 9PY. Telephone 01892-863-637.

U.S.A.

Dr. Paul Cheney, MD, The Cheney Clinic, P.O. Box 15675, Asheville, NC 28813-0675. Tel: 828-274-6665.

Dr. Charles Lapp, MD. Location 1: Hunter-Hopkins Center, 7421 Carmel Executive Park Dr., Charlotte, North Carolina 28226. Telephone: 704-543-9692. Fax: 704-543-8547. Location 2: Piedmont Medical Associates, 3400 Executive Drive, Suite 205, Raleigh, North Carolina 27609. Tel: 919-878 0900. Fax: 919-872 2456. Email: drlapp@drlapp.net.

Dr. Daniel L. Peterson, MD, Internal Medicine, CFS Specialist. Sierra Internal Medicine Associates, 926 Incline Way Suite 150, Incline Village, Nevada 89452. Telephone: 775-832-0989. Fax: 775-832-3046.

Appendix 2.

THE USE OF NIMODIPINE AS A TREATMENT FOR OTHER ILLNESSES

Nimodipine is used often and widely around the world. It is used for various purposes and researchers in several fields are also interested its benefits.

A. Brain aneurysms and strokes: Nimodipine is the only drug found to significantly preserve tissue by delivering oxygen to blocked areas of the brain following the leaking of a blood vessel in the brain. It was thought that it reduced the spasm of the blood vessels at the base of the brain but it is now theorized that the effects are due to the dilation of small brain vessels or the prevention of calcium overload in nerve cells. The suggested use is within 96 hours of the event, taking 60 mg every 4 hours up to 360 mg per day for 21 days. This drug is usually prescribed by hospital doctors. This is nimodipine's primary use. (Notes: 10, 12, 13, 38, 100, 131.)

There is an anecdotal report of continuous safe use of nimodipine for 12 years by a stroke patient that has regained the ability to speak, think, write, and walk. The anonymous patient, commenting on 3 February 2009, says he has taken it since 1997 and believes it to be a miracle drug. (Notes: 38.)

B. Dementia: It is known that changes in calcium regulation are an aspect of aging and has an important role in brain functions. Nimodipine is frequently prescribed for long term use in at least 23 countries worldwide, including Russia and several European countries, for cognitive impairment and dementia in old age.

In Europe, 70% of patients with age-related dementias showed improvements in memory deficits, attention, and verbal communication and less frequently show deterioration. This has been proven by group analysis of fifteen rigorous studies of up to 6 months. The improvement is greater with longer treatment and may not last when treatment stops. A dose of 90 mg performed better than lesser amounts and also better than 180 mg. It was well tolerated with few serious side effects. (Notes: 16, 46, 73, 95, 103, 107.)

C. Headaches: A nimodipine dosage of 120 to 180 mg per day has been shown in multiple studies to prevent migraines, thunderclap, and cluster headaches, and is thought to work by preventing vasoconstriction. It sometimes took 2 to 3 months to give benefit, the effectiveness sometimes diminished with subsequent treatments, but over 50% of the cases saw some benefit and some saw lasting benefit. The drug was well tolerated with no marked side effects. In some cases the effectiveness diminished. (Notes: 8, 34, 38, 42, 50, 75, 102, 115.)

D. Gulf War Syndrome: A study of 111 GWS patients treated with calcium channel blockers nimodipine, amlodipine or felodipine had an improvement in neurological signs such as heart-rate acceleration, blood vessel irritability, neuro-psychiatric and neuro-immune measurements. (Notes: 9.)

E. HIV/AIDS: In a study of 41 AIDS patients lasting 16 weeks, 90 mg and 300 mg per day of nimodipine safely reduced nervous system deterioration but only 300 mg per day improved neuro-psychiatric measurements. However, both were small changes. In a laboratory, it has been demonstrated that CCBs which cross the BBB halved the reproduction of the HIV virus in nerve tissue thereby reducing vision loss, spinal cord damage and dementia. Citing these benefits, two patent applications have included a CCB that crosses the blood-brain barrier in treatments for HIV/AIDS. The choices include diproteverine and Smith Kline drug number 9512, but nimodipine is preferred. (Notes: 63, 70, 71, 91.)

F. Eye health: Multiple trials have found that 60 mg of nimodipine improves the colour contrast sensitivity of vision and the ocular blood flow of patients with glaucoma. It may be possible to use nimodipine to prevent glaucoma caused by reduced blood flow to the eyes, because persons with a healthy vascular system gained more ocular blood flow than

those with advanced glaucoma in a trial of 90mg per day for 5 days. (Notes: 17, 74, 82.)

G. Tinnitus: 50 to 60 mg daily gave improvement to some patients with tinnitus. (Notes: 32.)

H: Brain lesions: A young woman with Susac's Syndrome which included brain lesions, problems with blood flow to her eyes, and hearing loss was given treatment with nimodipine and aspirin which reduced the severity and frequency of her symptoms. (Notes: 65.)

I. Parkinson's disease: An evaluation of 12 years of Danish medical records encompassing over 11,500 hypertension patients found that only those who had taken a DHP that cross the BBB showed a significant decrease in the risk of developing Parkinson's disease, presumably by acting on the calcium channels in the neurons and slowing or prohibiting the degeneration. (Notes: 30.)

J: Bi-polar disorder: Nimodipine is sometimes prescribed to manage the side effects of bipolar disorder medications but this benefit has not been scientifically proven. Many antipsychotic drugs induce involuntary movements and nimodipine may relieve these effects. The dosage range is 300 mg to 720 mg per day. (Notes: 1, 15.)

K. Hiccups: Nimodipine was used to treat intractable hiccups in one report. (Notes: 54.)

L: Panic attacks: In a small study on patients with panic attacks, the decrease in blood flow of arteries at the base of the skull was successfully treated with nimodipine, measured by transcranial Doppler ultrasonography. (Notes: 43.)

M: Fibromyalgia: M.E./CFS and fibromyalgia have many symptoms in common, many patients have both conditions, and the two are probably related immune system disorders. Pain is the predominant problem in people with fibromyalgia, whereas fatigue and cognitive dysfunction are the major complaints and pain a lesser symptom in most people with CFS. Dr. S. Silverman is a Clinical Professor of Rheumatology at UCLS/Cedars Sinai Hospital, California. He has found that some patients with FM have received benefit from nimodipine. (Notes: 67, 124.)

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The author is seeking further accounts from doctors and people with M.E.
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