

The NO/ONOO- Cycle as the Cause of Fibromyalgia and Related Illnesses:
Etiology, Explanation and Effective Therapy

Martin L. Pall*
School of Molecular Biosciences
Washington State University
Pullman WA 99164-4234 USA

martin_pall@wsu.edu
509-335-1246

ABSTRACT

Cases of fibromyalgia (FM) are initiated by any of four short-term stressors known to increase levels of nitric oxide. Related illnesses including chronic fatigue syndrome and multiple chemical sensitivity have similar patterns of case initiation. The chronic phase of illness is thought to be caused by a biochemical vicious cycle mechanism called the NO/ONOO- cycle. Various elements of this cycle are reported to be elevated in FM, including nitric oxide, oxidative stress, mitochondrial dysfunction, NF-kappa B activity, inflammatory cytokines activity, vanilloid activity and NMDA activity. This pattern confirms the presence of the NO/ONOO- cycle in FM. The NO/ONOO- cycle is also confirmed by:

- explanations of both symptoms and signs shared among this group of illnesses, where elements of the NO/ONOO- cycle can produce these symptoms and signs.
- explanations of the most specific symptoms characteristic of FM and also MCS and CFS, as being a consequence of tissue specific impact of NO/ONOO- cycle biochemistry; in FM the critical tissue involved in thought to be the thalamus. Evidence supporting a key thalamic role in FM is discussed.
- reported therapeutic improvements produced by agents and combinations of agents predicted to down-regulate NO/ONOO- cycle biochemistry.

The NO/ONOO- cycle paradigm challenges much of the conventional wisdom about FM. It argues that we understand the mechanism of FM sufficiently well that it should be considered a disease. It argues that both the etiology of FM and the origin of its symptoms should no longer be considered unexplained. It also argues that FM, like CFS and other members of this group of illnesses, can best be treated by combinations of agents down-regulating NO/ONOO- cycle biochemistry and that we do have effective treatments based on this principle.

INTRODUCTION

* School of Molecular Biosciences, Washington State University, Pullman, WA 99164-4234 USA

Chronic fatigue syndrome (CFS), fibromyalgia (FM) and multiple chemical sensitivity (MCS) are described as overlapping illnesses. They have high comorbidities, they share many common symptoms and they all show a common pattern of case initiation (1-12). Cases of each of them are often initiated by a short-term stressor, leading in turn, to chronic illness (12). These similarities have led multiple scientists to suggest that they may share a common etiology. For example, Donnay and Ziem suggest (4) that CFS, FM and MCS "may simply reflect different aspects of a common underlying medical condition". Buchwald and Garrity (2) inferred in a study of CFS, MCS and FM patients that: "Despite their different diagnostic labels, existing data, though limited, suggests that these illnesses may be similar if not identical conditions... ." Miller suggests that CFS, FM, MCS and certain other conditions share etiologic similarities (1), asking "Are we on the threshold of a new theory of disease?". Miller and others have suggested that posttraumatic stress disorder (PTSD) may also share a similar etiology (1,12-15). Gulf War syndrome appears to be a combination of all four of these diseases (16-20).

The only etiologic mechanism proposed for each of these is a vicious cycle mechanism involving elevated levels of nitric oxide and its oxidant product, peroxynitrite (12,21-30). This cycle may be initiated by a variety of diverse short-term stressors, including viral and bacterial infections, physical trauma, severe psychological stress, organic solvent exposure, and exposure to three classes of pesticides, organophosphorus/carbamate pesticides, organochlorine pesticides and pyrethroid pesticides). Each of these short-term stressors are known to be able to trigger responses that lead to increases in nitric oxide levels. Indeed, other initiating short-term stressors, including a protozoan infection, carbon monoxide exposure, thimerosal exposure and ciguatoxin exposure are also known or thought to act to increase nitric oxide levels, as well (12,22-27). The vicious cycle initiated by these nitric oxide increases is diagrammed in Fig. 1 and is centered on excessive levels of nitric oxide and its oxidant product peroxynitrite. We are now calling this vicious cycle the NO/ONOO- cycle (30)(pronounced no, oh no!), based on the structures of nitric oxide (NO) and peroxynitrite (ONOO-). Each of the arrows diagrammed in Fig. 1, represents one element of the cycle acting to increase the levels of another element of the cycle. The chronic nature of these diseases is thought to be caused by the NO/ONOO- cycle, propagating itself over time through the mechanisms represented by these arrows. Most of the individual mechanisms in the cycle are based on very well documented biochemistry (12,21-27,30), supporting the plausibility of the cycle as a whole. Cycle elements, as shown in Fig. 1, include not only nitric oxide and peroxynitrite, but also superoxide, oxidative stress, the transcription factor NF- κ B, the inflammatory cytokines (upper right hand corner), all three nitric oxide synthases (iNOS, nNOS, eNOS), intracellular calcium levels and two neurological receptors, the NMDA receptor and the vanilloid receptor (29,30). Peroxynitrite is known to attack a number of important components in mitochondria, particularly iron-sulfur proteins and nitric oxide and superoxide inhibit certain mitochondrial enzymes, as well (21,31). Superoxide and nitric oxide inhibit mitochondrial mechanisms, as well (32-37). Peroxynitrite also acts indirectly to impair mitochondrial function by stimulating poly ADP-ribose polymerase activity (38,39). Mitochondrial/energy metabolism dysfunction is a key consequence of the cycle and is also an important element in the cycle (21,25,30). It is the complexity of

the NO/ONOO- cycle and the difficulty in effectively lowering peroxynitrite levels, that make these diseases so difficult to treat.

The NO/ONOO- cycle etiology is based on five distinct principles (30):

1. NO/ONOO- cycle diseases are initiated by short-term stressors that increase the levels of nitric oxide and/or superoxide.
2. The chronic nature of these diseases is caused by the positive feedback loops that constitute the NO/ONOO- cycle.
3. Symptoms and signs of illness are produced by elevation of one or more elements of the cycle.
4. The basic mechanisms of the cycle are local, because nitric oxide, superoxide and peroxynitrite have limited half lives in biological tissues and diffuse only limited distances from their point of origin. In addition, most of the mechanisms involved in the cycle act at the cellular level, rather than systemically. The consequence of this, is that one tissue may be impacted by the cycle, but an adjacent tissue may be largely unimpacted, with the pattern of tissue impact in a particular patient being propagated over time essentially indefinitely.
5. These diseases are best treated by agents that down-regulate NO/ONOO- cycle biochemistry, and should not be limited to treatment aimed at symptomatic relief.

The central goal of this paper is to determine how well these five principles apply to FM. I will be asking each of the following questions:

1. Are cases of FM initiated by stressors that act to increase nitric oxide levels?
2. Are elements of the NO/ONOO- cycle elevated in FM?
3. Can the shared symptoms and signs of FM, CFS, MCS and PTSD be generated by the elements of the NO/ONOO- cycle?
4. Can the most specific symptom of FM, the widespread pain most characteristic of this disease, be generated by dysfunction of a specific tissue, presumably caused by the impact NO/ONOO- cycle on that tissue?
5. Does lowering of NO/ONOO- cycle biochemistry lead to measurable improvements in FM and in the related multisystem diseases?

I will answer each of these five questions with a yes.

ARE CASES OF FM INITIATED BY STRESSORS THAT ACT TO INCREASE NITRIC OXIDE LEVELS?

Many cases of FM are initiated by physical trauma (40-46), especially head and neck trauma (42). Head trauma is known to lead to increases in nitric oxide and peroxynitrite, acting mainly through increased NMDA activity (12,30). Physical trauma in other regions of the body is also reported to produce increases in nitric oxide (47-51) but the mechanism here is not known.

Other cases of FM are initiated by both viral and bacterial infection (40,52-56), with both types of these infections known to produce increases in nitric oxide (21). Infection mainly acts to increase nitric oxide levels through iNOS induction (21) whereas head trauma acts through NMDA stimulation and consequent nNOS activation (12,30). It can be seen from this that distinct forms of nitric oxide synthase may be involved, with the common response being an increase in nitric oxide and presumably also its oxidant product, peroxynitrite.

Still other cases of FM are initiated by severe psychological stress (45,58-62) and such stress in animal models is known to produce increases in NMDA activity and nitric oxide (12).

Additional cases of FM are considered to be secondary to autoimmune diseases, especially lupus and rheumatoid arthritis (63,64). Both of these autoimmune diseases are characterized by increases in nitric oxide and peroxynitrite (65-67), again suggesting a common pattern of FM case initiation.

In summary, there are at least five classes of stressor that initiate cases of FM and all five are known to produce increases in nitric oxide. The five are physical trauma, viral infection, bacterial infection, severe psychological stress and autoimmune diseases. FM fits the first principle of the NO/ONOO- cycle because cases are often initiated by stressors increasing nitric oxide levels.

ARE THE ELEMENTS OF THE NO/ONOO- CYCLE ELEVATED IN FM?

There are multiple elements of the NO/ONOO- cycle that have been studied in the chronic phase of FM and have been reported to be elevated when compared with normal controls. These are as follows:

Markers of oxidative stress have been studied in FM and have been consistently been shown to be elevated (68-75).

Mitochondrial/energy metabolism dysfunction have been reported in multiple studies of FM, using diverse approaches to such study (76-85).

The inflammatory cytokines also are reported to be elevated in several studies (86-91).

Three types of studies suggest that NMDA receptor activity is elevated in FM. The first of these is that studies with three different NMDA receptor antagonists produced clinical improvement in cases of FM (92-100). In addition, two research groups have reported that glutamate levels in the cerebrospinal fluid of FM patients are elevated, suggesting excessive NMDA stimulation (101,102). Finally, Smith and coworkers (103) reported that both monosodium glutamate and aspartame, excitotoxins leading to NMDA stimulation, had an important role in maintaining some cases of FM; in these cases placing patients on a diet devoid of these and related excitotoxins led to recovery from the symptoms of FM. All three of these types of studies support the inference that

NMDA activity is elevated in FM. The NMDA antagonist studies and excitotoxin studies support the view that down-regulating NO/ONOO- cycle biochemistry is useful in the treatment of FM.

Two studies of FM reported increased synthesis of nitric oxide (101,104), consistent with elevation of another important element of the NO/ONOO- cycle. However, a third study, measuring nitrosothiol levels inferred that nitric oxide levels were lower in FM than in controls (105). However, nitrosothiols may not always be a good marker for nitric oxide synthesis because nitrosothiols are reported to react with both peroxynitrite and superoxide (106,107) and thus may be lowered by other aspects of NO/ONOO- cycle biochemistry. Because two studies provide support for increased nitric oxide synthesis and because elevated NMDA activity and elevated inflammatory cytokine levels are both expected to increase nitric oxide levels, it may be inferred that nitric oxide levels are elevated in FM.

There are three studies suggesting that vanilloid receptor activity is elevated in FM; these have used capsaicin, the specific vanilloid receptor agonist, to demonstrate elevated vanilloid receptor responsiveness (108-110).

There are no studies measuring NF- κ B activity in FM.

It can be seen, from the above, that multiple components of the NO/ONOO- cycle are elevated in FM, providing support for the view that FM is a NO/ONOO- cycle disease.

CAN THE SHARED SYMPTOMS AND SIGNS OF FM BE GENERATED BY THE ELEMENTS OF THE NO/ONOO- CYCLE?

Fifteen symptoms and signs found in FM and shared with the other multisystem diseases are listed in Table 1. In each case, one or more mechanisms by which these may be generated involve elements of the NO/ONOO- cycle (see ref 30 for citations). It follows that many diverse symptoms and signs may come from a NO/ONOO- cycle mechanism.

It should be pointed out that these mechanisms are put forth as plausible mechanisms, not as established mechanisms in FM and these related multisystem diseases. However, such plausible mechanisms provide explanations for these diverse symptoms, such that they should no longer be considered unexplained.

CAN WIDESPREAD PAIN OF FM BE GENERATED BY DYSFUNCTION OF A SINGLE ORGAN?

The widespread pain that is the most characteristic symptom of FM produces a major challenge for the NO/ONOO- cycle as an explanatory model. Because the main mechanisms of the cycle are local, it seems highly unlikely that the pain is generated solely from widespread body impact of the NO/ONOO- cycle. If this were the case, one would expect many cases where certain regions of the body were characterized by excessive pain but other regions were not. However, the widespread, excessive pain in

FM appears almost like a quantum event, albeit one with variable quantitative differences from one patient to another. The studies of Staud and coworkers (111) present another, related challenge to the NO/ONOO- cycle model. They report that the pain processing in the various dorsal horn regions of the spinal cord is up-regulated in FM, showing that there are changes in pain processing up and down the spinal cord. Again, there appears to be a widespread change in pain processing that is characteristic of FM.

The question raised by the NO/ONOO- cycle mechanism is whether the impact on a particular organ of the body might lead to widespread increased pain sensitivity? The general answer seems to be that there is a change in the control of pain processing due to changes in the central nervous system (111-117), but the question is what organ may be involved and how? I suggest that the organ involved may be the thalamus and that thalamic involvement may be the key feature that distinguishes FM from other, related illnesses not characterized by such widespread pain sensitivity. The thalamus has descending neurons, known as lamina I neurons, that act primarily to inhibit pain processing in the various dorsal horn regions of the spinal cord (118-120). In this way, thalamic dysfunction may be able to produce the increased pain processing reported earlier (111). A recent study reported a deficiency in pain inhibitory activity in FM (121). Such thalamic involvement in FM has been suggested by Larson and Kovacs (122), by Henriksson (123) and also by Staud (124). The main difference between my suggestion here and those of these other researchers is that I suggest the chronic thalamic dysfunction is produced by the impact of the NO/ONOO- cycle on the thalamus.

Several brain scan studies of FM patients have reported thalamic changes (125-128), providing support for its involvement in FM. Substantial thalamic involvement in FM is also suggested by the observations of Larson and coworkers (129) reporting mast cell activation in the thalamus in FM. Mast cell activation is stimulated by both vanilloid receptor stimulation and by nitric oxide, both elements of the NO/ONOO- cycle mechanism.

The anatomical location of the thalamus may make it particularly sensitive to the head and neck trauma that often initiates cases of this disease. The thalamus is located as essentially a linear extension of the spinal cord, so both its location and the many neurons connecting the spinal cord with the thalamus may be expected to make it sensitive to head and neck physical trauma. It is plausible, therefore, that head and neck trauma may initiate NO/ONOO- cycle biochemistry in the thalamus.

In summary, then, the chronic widespread excessive pain characteristic of FM may be generated by the impact of the NO/ONOO- cycle on the thalamus, whereas other symptoms of FM and related multisystem diseases may be generated by the impact of the cycle in additional regions of the brain and other areas of the body.

THERAPY

The fifth principle of the NO/ONOO- cycle is that diseases caused by the cycle are best treated by using agents that down-regulate NO/ONOO- cycle biochemistry. The

complexity of the cycle and the limited effectiveness of scavengers for peroxynitrite, the most central element of the cycle, provide an explanation for the difficulty in treating these diseases. We have no magic bullet for such treatment, and may never have such an individually effective agent.

In Chapter 15 of my book (30), I discuss 30 different agents or classes of agents that are predicted to down-regulate NO/ONOO- cycle biochemistry and are available today (summarized on Table 2). The agents act in diverse fashions and are expected to act both individually with each other to lower the NO/ONOO- cycle. Of these 30, there is clinical trial data supporting the effectiveness of 12 in the treatment of FM, CFS and/or MCS (summarized in Table 2). There are clinical observations and/or anecdotal evidence suggesting efficacy for another 6 of these. Most of these individually produce fairly modest improvements, however, raising the question of whether they will be more effective when used in complex combinations.

I also discuss clinical protocols developed by five different physicians on these multisystem diseases (30), each of which use multiple agents or classes of agents predicted to down-regulate NO/ONOO- cycle biochemistry (summarized in Tables 3-7). Two of these, the protocols of Teitelbaum (130,131) and of Nicolson (132,133) have been tested in clinical trials and have been reported to produce statistically significant improvement. Of these protocols, Teitelbaum's is the only one tested in FM. His, Cheney's, and Petrovic's protocol has been used to treat CFS patients. Nicolson's has been used to treat older patients with unexplained chronic fatigue but who also have several symptoms common in CFS patients (132,133). The protocol of Ziem is one that I have been instrumental in designing, has been tested on her chemically injured, chemically sensitive patients. Ziem does not use the diagnosis of MCS for these patients, arguing that many of them are better diagnosed as having toxic encephalopathy. Ziem discusses her criticisms of the name MCS on her web site (chemicalinjury.net).

What can be seen is that each of these treatment protocols uses from 14 to 18 agents or classes of agents predicted to down-regulate NO/ONOO- cycle biochemistry. I argue that this is not a coincidence. Rather it seems apparent that:

- The NO/ONOO- cycle mechanism makes useful predictions for therapy of these diseases; agents predicted to be useful by down-regulating this biochemistry often appear to be useful individually and collectively in the treatment of these diseases.
- Individual agents generally produce only modest improvement, but these combinations of agents produce much more substantial clinical improvement, according to these physicians. This again supports the view that the NO/ONOO- cycle produces useful predictions that are of great value in designing effective treatment protocols.
- Conversely, the efficacy of these agents and combinations of agents, provides clinical support for the NO/ONOO- cycle mechanism of these diseases, support that is not available for any alternative mechanism for this group of multisystem diseases.

It should be noted that these agents are clearly most effective when used in combination with avoidance of stressors that are predicted to up-regulate NO/ONOO- cycle biochemistry. These stressors include excitotoxins, food allergens in the many who are sensitive to certain foods, chemical exposure in MCS patients, excessive exercise in CFS patients and psychological stress in PTSD patients.

CONCLUSION

Clearly the NO/ONOO- cycle mechanism challenges all or almost all of the conventional wisdom about FM and this whole group of multisystem diseases. It argues that they are diseases, with an understandable morbid process and, indeed, etiology. It argues that the shared symptoms and signs of illness are explainable in terms of the etiologic mechanism. It argues that the specific symptoms of each of these diseases is interpretable as being caused by the impact of this biochemistry on certain regions of the body. It provides the first useful overall approach to the therapy of these diseases, a therapeutic approach that is particularly valuable because it appears to provide useful therapy for not just one but rather several of these overlapping diseases.

In Chapter 16 of my book (30), I list a dozen explanations provided for previously puzzling features of these diseases, none of which were explained previously. The fit between this mechanism and these features is truly extraordinary:

1. It provides explanations for the etiology of not just one but all four of these multisystem diseases.
2. It explains their chronic nature.
3. It explains how cases of each can be initiated by 12 diverse and distinct stressors.
4. It explains the diverse biochemical and physiological properties of the chronic phase of these diseases.
5. It explains how many different agents or groups of agents may produce reported improvements and how the treatment protocols of five different physicians may lead to major improvements in sufferers.
6. It explains 16 of the shared symptoms and signs of these diseases, symptoms and signs that have repeatedly been described as being previously unexplained.
7. It explains the symptoms that are specific for each type of disease, symptoms that can be explained by the influence of the NO/ONOO- cycle on specific tissues.
8. It explains their high comorbidity with each other.
9. It explains their high comorbidity with such well-accepted diseases as tinnitus, asthma, migraine, lupus and rheumatoid arthritis.
10. It explains 11 distinct puzzling feature of MCS, only one of which was adequately explained previously.
11. It explains the properties of animal models of CFS, MCS and PTSD, each of which provides evidence, in turn, supporting a NO/ONOO- cycle etiology.
12. It explains the stunning qualitative and quantitative variation in symptoms from one patient to another.

The NO/ONOO- cycle mechanism argues that this group of previously puzzling diseases should no longer be considered unexplained. The observations with agents predicted to down-regulate NO/ONOO- cycle biochemistry argue that we now have therapeutic protocols that are effective because they lower the basic mechanism of disease.

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Table 1

Symptom/ Sign	Explanation based on elevated nitric oxide/peroxynitrite theory
energy metabolism /mitochondrial dysfunction	Inactivation of several proteins in the mitochondrion by peroxynitrite; inhibition of some mitochondrial enzymes by nitric oxide and superoxide
oxidative stress	Peroxynitrite, superoxide and other oxidants
PET scan changes	Energy metabolism dysfunction leading to change transport of probe; changes in perfusion by nitric oxide, peroxynitrite and isoprostanes
SPECT scan changes	Depletion of reduced glutathione by oxidative stress; perfusion changes as under PET scan changes
Low NK cell function	Superoxide and other oxidants acting to lower NK cell function
Elevated cytokines	NF- κ B stimulating of the activity of inflammatory cytokine genes
Anxiety	Excessive NMDA activity in the amygdala
Depression	Elevated nitric oxide leading to depression; cytokines and NMDA increases acting in part or in whole via nitric oxide.
Cognitive/learning and memory dysfunction	Lowered energy metabolism in the brain (which is very susceptible to such changes); excessive NMDA activity and nitric oxide levels and their effects of learning and memory
Multiorgan pain	All components of cycle have a role, acting in part through nitric oxide and cyclic GMP elevation
Fatigue	Mitochondrial/energy metabolism dysfunction
Sleep disturbance	Sleep impacted by inflammatory cytokines, NF- κ B activity and nitric oxide
Orthostatic intolerance	Two mechanisms: Nitric oxide-mediated vasodilation leading to blood pooling in the lower body; nitric oxide-mediated sympathetic nervous system dysfunction
Irritable bowel syndrome	Sensitivity and other changes produced by excessive vanilloid and NMDA activity, increased nitric oxide
Intestinal permeabilization leading to food allergies	Permeabilization produced by excessive nitric oxide, inflammatory cytokines, NF- κ B activity and peroxynitrite; peroxynitrite acts in part by stimulating poly ADP-ribose polymerase activity

Table 2. NO/ONOO- Cycle Summary of Individual Agents or Classes of Agents

<u>Agent or Class of Agents</u>	<u>Clinical Trial Data or Clinical Observation/Anecdotal Reports</u>
Vitamin C (ascorbic acid)	Clinical Trial Data
Tocopherols/Tocotrienols	Anecdotal Reports
Selenium	None
Carotenoids	None
Flavonoids	Clinical Trial Data
Reductive stress relieving agents	Clinical Trial Data
Mitochondrial regeneration agents	Clinical Trial Data
L-Carnitine/Acetyl-L-carnitine	Clinical Trial Data
Hydroxocobalamin/B ₁₂	Clinical Trial Data
Folic acid	Clinical Trial Data
Vitamin B ₆ /pyridoxal phosphate	Anecdotal Reports
Riboflavin	None
Other B vitamins	None
Glutathione/glutathione precursors	Clinical Observations
□-Lipoic acid	None
Magnesium	Clinical Trial Data
SOD minerals/zinc,manganese, copper	None
NMDA antagonists	Clinical Trial Data
Riluzole	None
Taurine	None
Inosine/uric acid	None
Long chain omega-3 fatty acids	Clinical Trial Data
Agents that lower NF-□B activity	Anecdotal Reports
Curcumin	None
Algal supplements	Clinical Trial Data
Hyperbaric oxygen	Clinical Trial Data
Minocycline and Other Tetracyclines	Clinical Observations
Creatine	None
Lowered vanilloid activity	None
Carnosine	None
TRH	Clinical Observation

Table 3. Agents from Nicolson Protocol Predicted to Down-Regulate NO/ONOO-Cycle Biochemistry

Other phosphatidyl polyunsaturated lipids—this and the phosphatidyl choline are predicted to help restore the oxidatively damaged mitochondrial inner membrane
Magnesium—lowers NMDA activity, may aid in energy metabolism
Taurine—antioxidant activity and lowers excitotoxicity including NMDA activity
Artichoke extract—as flavonoid source?
Spirulina—blue-green alga is a concentrated antioxidant source

Natural vitamin E—does not tell us whether this includes γ -tocopherol or tocotrienols
Calcium ascorbate—vitamin C
α -Lipoic acid—important antioxidant, key role in regeneration of reduced glutathione, but also has role in energy metabolism
Vitamin B ₆ —balance glutamate and GABA levels, lowers excitotoxicity
Niacin—role in energy metabolism
Riboflavin—important in reduction of oxidized glutathione back to reduced glutathione; also has important role in mitochondrial function
Thiamin—role in energy metabolism
Vitamin B ₁₂ —as nitric oxide scavenger?
Folic acid—lowers nitric oxide synthase uncoupling

Table 4. Agents from Teitelbaum Protocol Predicted to Down-Regulate NO/ONOO-Cycle Biochemistry

Daily energy B-complex—B vitamins including high dose B ₆ , riboflavin, thiamine, niacin and also folic acid. These fall into four categories that I have listed earlier in the chapter
Betaine hydrochloride (HCl)—lowers reductive stress, hydrochloride form should only be taken by those deficient in stomach acid
Magnesium as magnesium glycinate and magnesium malate—lowers NMDA activity—often uses magnesium injections
α-Lipoic acid—important antioxidant helps regenerate reduced glutathione
Vitamin B ₁₂ IM injections, 3 mg injections (does not state whether this is hydroxocobalamin)—may act as potent nitric oxide scavenger
Eskimo fish oil—excellent source of long chain omega-3 fatty acids. Lowers iNOS induction, anti-inflammatory
Vitamin C
Grape seed extract (flavonoid)
Vitamin E, natural—does not state whether this includes γ-tocopherol or tocotrienols
Physician's protein formula, used as glutathione precursor
Zinc—antioxidant properties and copper/zinc superoxide dysmutase precursor
Acetyl-L-carnitine—important for restoring mitochondrial function
Coenzyme Q10—both important antioxidant properties and stimulates mitochondrial function

Table 5. Agents from Cheney Protocol Predicted to Down-Regulate NO/ONOO-Cycle Biochemistry

High dose hydroxocobalamin (B12) injections—nitric oxide scavenger
Whey protein—glutathione precursor
Guaifenesin—vanilloid antagonist?
NMDA blockers
Magnesium—lowers NMDA activity
Taurine—antioxidant and acts to lower excitotoxicity including NMDA activity
GABA agonists—GABA acts as an inhibitory neurotransmitter to lower NMDA activity—these include the drug neurotin (gabapentin)
Histamine blockers—mast cells which release histamine are activated by both nitric oxide and vanilloid stimulation (Chapter 7) and may therefore be part of the cycle mechanism
Betaine hydrochloride (HCl)—Betaine lowers reductive stress, the hydrochloride form should only be used in those with low stomach acid. Betaine (trimethylglycine) is also listed separately in the protocol description
Flavonoids, including “bioflavonoids,” olive leaf extract, organic botanicals, hawthorn extract
Vitamin E (forms not listed)
Coenzyme Q10—acts both as antioxidant and to stimulate mitochondrial function
α -lipoic acid
Selenium
Omega-3 and -6 fatty acids
Melatonin—as an antioxidant
Pyridoxal phosphate—improves glutamate/GABA ratio
Folic acid—lowers uncoupling of nitric oxide synthases

Table 6. Agents from Petrovic Protocol Predicted to Down-Regulate NO/ONOO-Cycle Biochemistry

Valine and isoleucine—branched chain amino acids known to be involved in energy metabolism in mitochondria, and may be expected, therefore, to stimulate energy metabolism; modest levels may also lower excitotoxicity
Pyridoxine (B ₆)—improves balance between glutamate and GABA, lowers excitotoxicity
Vitamin B ₁₂ in the form of cyanocobalamin—cyanocobalamin is converted to hydroxocobalamin in the human body but the latter form will be more active as a nitric oxide scavenger, since it does not require such conversion
Riboflavin—helps reduce oxidized glutathione back to reduced glutathione
Carotenoids (alpha-carotene, bixin, zeaxanthin and lutein)-lipid (fat) soluble peroxynitrite scavengers
Flavonoids (flavones, rutin, hesperetin and others)
Ascorbic acid (vitamin C)
Tocotrienols—forms of vitamin E reported to have special roles in lowering effects of excitotoxicity
Thiamine (aneurin)—B vitamin involved in energy metabolism
Magnesium—lowers NMDA activity; may aid energy metabolism
Zinc—precursor of SOD
Betaine hydrochloride (HCl)—lowers reductive stress, hydrochloride form should only be used by those deficient in stomach acid
Essential fatty acids including long chain omega-3 fatty acids
Phosphatidyl serine—reported to lower iNOS induction

Table 7. Agents from Pall/Ziem Protocol Predicted to Down-Regulate NO/ONOO-Cycle Biochemistry

Nebulized, inhaled reduced glutathione
Nebulized, inhaled hydroxocobalamin (some use sublingual)
Mixed, natural tocopherols including γ -tocopherol
Buffered vitamin C
Magnesium as malate
Four different flavonoid sources: Ginkgo biloba extract, cranberry extract, silymarin, and bilberry extract
Selenium as selenium-grown yeast
Coenzyme Q10
Folic acid
Carotenoids including lycopene, lutein and β -carotene
α -Lipoic acid
Zinc (modest dose), manganese (low dose) and copper (low dose)
Vitamin B ₆ in the form of pyridoxal phosphate
Riboflavin 5'-phosphate (FMN)
Betaine (trimethylglycine)

Dr. Ziem has recently added two additional agents: green tea extract and acetyl L-carnitine.

Figure 1. NO/ONOO- Cycle Mechanism

Each arrow represents one or more mechanisms by which one element of the cycle increases the activity/level of another element of the cycle. The vicious cycle nature of the overall NO/ONOO- cycle mechanism is indicated by the many cyclical patterns shown by these combinations of arrows. This figure is taken with permission from the author's web site (http://molecular.biosciences.wsu.edu/faculty/pall/pall_cfs.htm).