



## Accurate Clinic

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## Accurate Education

### ***Brief Review of the Key Supplements in the 4-D Protocol for Pain***

#### **How These Supplements Work in Your Body**

This guide explains how each supplement in the 4-D protocol helps address inflammation, oxidative stress (cell damage from harmful molecules), mitochondrial dysfunction (problems with your cells' energy factories), and pain sensitization (when the nervous system becomes overly sensitive to pain).

**Remember**, the strength of the 4-D protocol lies in completing an individualized assessment of how each of these four key domains (“Demons”) noted below impact each patient. Determining how each of these areas impact the individual is assessed by a number of factors, including the results of blood work, answers on questionnaires identification of symptoms, underlying medical conditions, co-administration of prescription and non-prescription medications, including nutraceuticals - all contribute to determining individualized nutraceutical treatment.

#### **The Four Key Domains These Supplements Target**

- **Systemic Inflammation:** Body-wide inflammation that affects multiple organs and systems
- **Neuroinflammation:** Inflammation specifically in the brain and nervous system
- **Oxidative Stress:** Damage to cells caused by unstable molecules called free radicals
- **Mitochondrial Dysfunction:** Problems with the parts of your cells that produce energy
- **Peripheral and Central Sensitization:** Sensitization develop as a consequence of pathologic activity of the above four domains, causing nerves and spinal cord to become overly sensitive, magnifying pain.

### **The 20 Nutraceuticals**

#### **1. Acetyl-L-Carnitine (ALC)**

**What it does:** Helps your mitochondria (cell energy factories) work better and protects nerve cells. It reduces inflammation in both your body and brain, fights oxidative stress, and helps relieve nerve pain. ALC also supports the production of energy in your cells and helps maintain healthy brain function.

#### **2. Agmatine (Agmatine Sulfate)**

**What it does:** A natural compound made from the amino acid L-arginine that acts as a powerful neuromodulator. Agmatine selectively blocks a specific type of pain receptor in your spinal cord

(the GluN2B subunit of the NMDA receptor), which helps prevent the maladaptive nerve changes that keep chronic pain going — without causing the sedation or motor problems seen with other NMDA blockers. It also inhibits nitric oxide synthase (an enzyme that can worsen pain signaling when overactive), activates your body's master antioxidant pathway (Nrf2), and reduces oxidative stress and inflammation. Agmatine also supports mitochondrial health by helping maintain the balance of mitochondrial fusion and fission. In a clinical trial of patients with lumbar disc-associated radiculopathy, oral agmatine sulfate (2.67 g/day for 14 days) significantly improved pain scores and quality of life compared to placebo. Agmatine crosses the blood-brain barrier after oral dosing, with an oral bioavailability of approximately 29–35%.

### 3. Alpha-Lipoic Acid (ALA)

**What it does:** Acts as a powerful antioxidant that works in both water and fat parts of your cells. It helps regenerate other antioxidants like glutathione and vitamin E, reduces inflammation throughout your body and brain, and improves how your mitochondria produce energy. ALA is particularly helpful for protecting nerves from damage.

### 4. Boswellia

**What it does:** Reduces inflammation by blocking specific inflammatory pathways in your body. It helps calm down overactive immune cells in your brain (microglia) and reduces the production of inflammatory chemicals. Boswellia also protects against oxidative stress and may help reduce pain sensitivity.

### 5. CoQ10 (Coenzyme Q10)

**What it does:** Essential for energy production in your mitochondria and acts as a powerful antioxidant. It helps protect cell membranes from damage, reduces inflammation, and supports heart and muscle function. CoQ10 levels naturally decrease with age, making supplementation important for maintaining cellular energy.

### 6. Curcumin

**What it does:** A powerful anti-inflammatory compound that works through multiple pathways. It reduces inflammation in both your body and nervous system, protects against oxidative stress, and helps prevent overactive pain signals in your spinal cord. Curcumin also supports healthy brain function and may help reduce chronic pain.

### 7. Magnesium L-Threonate

**What it does:** Blocks pain receptors in your spinal cord (NMDA receptors) that contribute to central sensitization. It reduces neuroinflammation, supports mitochondrial function, and helps regulate nerve signals. Magnesium also has calming effects on your nervous system and supports hundreds of biochemical reactions in your body.

### 8. Melatonin

**What it does:** Beyond helping with sleep, melatonin is a powerful antioxidant that protects your mitochondria. It reduces inflammation in your brain, fights oxidative stress, and helps maintain healthy mitochondrial function. Melatonin also supports your body's natural antioxidant systems.

## 9. NAC (N-Acetyl Cysteine)

**What it does:** Helps your body produce glutathione, your most important internal antioxidant. It reduces oxidative stress and inflammation, supports mitochondrial health, and helps protect nerve cells. NAC also helps regulate glutamate, a brain chemical that can cause problems when levels are too high.

## 10. Nicotinamide Riboside (NR)

**What it does:** Boosts NAD+ levels, which are essential for energy production and cellular repair. It improves mitochondrial function, reduces inflammation, and supports healthy aging. NR helps your cells produce more energy and may protect against age-related decline in cellular function.

## 11. Omega-3 (EPA/DHA)

**What it does:** Reduces inflammation throughout your body and brain by producing anti-inflammatory molecules. EPA and DHA help calm overactive immune cells, reduce pain signaling, and support brain health. They also help resolve inflammation naturally and protect nerve cells from damage.

## 12. PEA (Palmitoylethanolamide)

**What it does:** A natural compound your body makes that reduces pain and inflammation. It works by calming down mast cells and glial cells (immune cells in your nervous system), reducing the production of inflammatory chemicals, and helping to normalize pain sensitivity. PEA is particularly effective for nerve pain.

## 13. Quercetin

**What it does:** A plant compound that fights oxidative stress and reduces inflammation. It helps protect your mitochondria, reduces the activation of inflammatory pathways in your brain, and supports your body's natural antioxidant defenses. Quercetin also helps remove damaged mitochondria through a process called mitophagy.

## 14. Resveratrol

**What it does:** Activates protective proteins (sirtuins) that support mitochondrial health and reduce inflammation. It fights oxidative stress, protects nerve cells, and helps maintain healthy mitochondrial function. Resveratrol also supports healthy aging and may protect against neurodegeneration.

## 15. Sulforaphane

**What it does:** Activates your body's master antioxidant pathway (Nrf2), which turns on genes that protect against oxidative stress. It reduces neuroinflammation, supports mitochondrial health, and helps your cells defend against damage. Sulforaphane is found in broccoli sprouts and other cruciferous vegetables.

## 16. Taurine

**What it does:** Supports mitochondrial function, reduces oxidative stress, and has anti-inflammatory effects. It helps regulate calcium in your cells, protects nerve cells, and supports healthy brain function. Taurine also helps maintain the balance of neurotransmitters in your brain.

## 17. B-Complex Vitamins (including B12)

**What it does:** Essential for energy production in your mitochondria and nerve function. B vitamins reduce inflammation, support the production of neurotransmitters, and help protect nerve cells. They work together synergistically, meaning they're more effective when taken together than individually.

## 18. Vitamin D3

**What it does:** Reduces inflammation in both your body and brain, supports immune function, and protects nerve cells. It helps regulate inflammatory pathways, reduces oxidative stress, and may help reduce pain sensitivity. Vitamin D3 also supports brain health and mood.

## 19. P5P (Pyridoxal-5-Phosphate)

**What it does:** The active form of vitamin B6 that's essential for mitochondrial function and energy production. It supports the production of neurotransmitters, helps maintain healthy metabolism, and protects against oxidative stress. P5P is particularly important for mitochondrial health.

## 20. D-Ribose

**What it does:** A simple sugar that helps your cells produce ATP (cellular energy). It supports mitochondrial energy production and may help reduce fatigue. D-ribose provides the building blocks your cells need to make energy molecules and nucleotides.

## Recommended Synergies: How These Supplements Enhance Each Other

These nutraceuticals are designed to work together. Below are the key synergistic groupings in the 4-D protocol, organized by the body system they support. Understanding these pairings can help appreciate why the protocol uses multiple supplements rather than just one or two.

### Synergy 1 — Dual NMDA Receptor Blockade for Central Sensitization:

#### Agmatine + Magnesium L-Threonate

Central sensitization — when your spinal cord becomes "wound up" and amplifies pain signals — is driven largely by NMDA receptors. **Agmatine** and magnesium both block these receptors, but they do so through different and complementary mechanisms. Agmatine preferentially targets the GluN2B subunit of the NMDA receptor in the spinal cord dorsal horn, the specific subunit most involved in chronic pain neuroplasticity.

It also works downstream of the receptor by disrupting the connection between the NMDA receptor and nitric oxide synthase (the PSD95-nNOS pathway), reducing harmful nitric oxide production. **Magnesium**, on the other hand, acts as a voltage-dependent channel blocker of the

NMDA receptor — it physically plugs the receptor's ion channel. Together, these two agents provide layered NMDA receptor inhibition: magnesium blocks the channel itself, while agmatine selectively dampens the GluN2B-mediated signaling and downstream nitric oxide cascades that sustain chronic pain. Importantly, agmatine achieves this without the sedation or motor impairment seen with non-selective NMDA blockers.

## **Synergy 2 — Antioxidant Network:**

### **ALA + NAC + Quercetin + Sulforaphane + Agmatine**

These five supplements form an interconnected antioxidant defense system. **ALA** regenerates glutathione by activating the Nrf2 antioxidant pathway and upregulating the enzymes needed for glutathione production. **Glutathione** is the body's "master antioxidant" because it is produced in the body, found in every cell, and recycles other antioxidants like vitamins C and E. It is vital for detoxification and reducing oxidative stress,

**NAC** provides the raw material (cysteine) your body needs to build glutathione. Together, ALA and NAC boost your glutathione levels more effectively than either one alone. **Sulforaphane** further amplifies this system by powerfully activating the same Nrf2 master switch, while **quercetin** provides direct free-radical scavenging and helps remove damaged mitochondria.

**Agmatine** adds to this network by independently activating the Nrf2/HO-1 pathway through the PI3K/Akt signaling cascade, providing an additional route to upregulate your body's own antioxidant defenses. The result is a layered defense: NAC supplies the building blocks, ALA, sulforaphane, and agmatine turn on the production machinery through overlapping but distinct pathways, and quercetin provides additional direct protection.

## **Synergy 3 — Anti-Inflammatory Powerhouse:**

### **Curcumin + Omega-3 (EPA/DHA) + PEA + Boswellia + Agmatine**

These five supplements target inflammation through different but complementary pathways, providing broader coverage than any single agent. **Curcumin** inhibits the NF-κB inflammatory pathway and reduces COX-2 activity. **Omega-3** fatty acids produce specialized pro-resolving mediators (SPMs) that actively resolve inflammation rather than just suppressing it. **PEA** calms mast cells and glial cells through the PPAR-α receptor. **Boswellia** blocks 5-lipoxygenase, reducing leukotriene production. **Agmatine** contributes by inhibiting nitric oxide synthase (reducing inflammatory nitric oxide) and suppressing the HMGB1/RAGE/TLR4/NF-κB signaling cascade — a key inflammatory pathway in the nervous system. By targeting these distinct pathways simultaneously, the combination provides comprehensive inflammation control that addresses both peripheral and central (brain and spinal cord) inflammation.

## **Synergy 4 — Mitochondrial Energy Restoration:**

### **CoQ10 + NR + ALC + D-Ribose + Agmatine + Taurine**

Mitochondrial dysfunction — when your cells' energy factories don't work properly — is a key driver of chronic pain and fatigue. This group of supplements addresses energy production at multiple steps. **CoQ10** is a critical component of the electron transport chain (the final step of energy production). **NR** boosts NAD+ levels, which are needed to fuel the earlier steps of energy metabolism. **ALC** shuttles fatty acids into mitochondria for fuel and supports the production of acetyl-CoA. D-Ribose provides the sugar backbone needed to build ATP molecules. **Taurine** helps regulate calcium within mitochondria and stabilizes mitochondrial membranes. **Agmatine** supports mitochondrial health by modulating mitochondrial dynamics — helping maintain the proper balance between mitochondrial fusion and fission, and preventing excessive opening of the mitochondrial permeability transition pore (which can trigger cell

damage). Together, these supplements address energy production from raw materials through to final ATP output, while protecting the mitochondria themselves.

### **Synergy 5 — Neuroprotection and Pain Neuroplasticity:**

#### **Agmatine + PEA + ALC + B-Complex + Vitamin D3 + Melatonin**

Chronic pain involves maladaptive changes in your nervous system — your nerves and brain essentially "learn" to amplify pain signals. This group works together to protect nerve cells and reverse these harmful changes. **Agmatine** is uniquely positioned here because it has been shown to reverse the neuroplasticity (maladaptive nerve changes) that maintains chronic pain, persistently reversing established pain hypersensitivity in preclinical models for over 266 days. **PEA** calms the glial cells that drive neuroinflammation. **ALC** supports nerve cell energy and repair. **B vitamins** are essential for myelin (nerve insulation) maintenance and neurotransmitter production. **Vitamin D3** regulates neuroinflammatory pathways and supports nerve cell survival. **Melatonin** provides potent antioxidant protection specifically within mitochondria of nerve cells. Together, these agents protect nerves from multiple angles while agmatine works to reverse the central sensitization that keeps chronic pain going.

### **Synergy 6 — Glutamate and Excitotoxicity Control:**

#### **NAC + Agmatine + Magnesium + Taurine**

Excessive glutamate (an excitatory brain chemical) can overstimulate nerve cells and worsen pain. **NAC** helps regulate glutamate levels by supporting the cystine-glutamate antiporter. **Agmatine** and **magnesium** both block NMDA receptors (which glutamate activates) through complementary mechanisms described above. **Taurine** acts as an inhibitory neuromodulator, helping to counterbalance excessive excitatory signaling. This four-agent approach addresses glutamate overactivity from multiple directions: reducing glutamate levels (NAC), blocking its receptor (agmatine and magnesium), and providing inhibitory counterbalance (taurine).

## **Important Notes**

### **A NOTE ABOUT THE EVIDENCE**

These supplements have strong scientific research supporting their use, but no clinical trial has yet tested this specific four-supplement combination for reducing pain. Your doctor is recommending this approach based on the best available evidence and will monitor your response carefully. Your feedback is essential to making this program work.

- These supplements are designed to address the root causes of one's symptoms, not just mask them
- Benefits may take several weeks to become noticeable as cells repair and function improves
- Consistency in taking the supplements is important for optimal results
- Always take these supplements as directed by your healthcare provider
- Keep your healthcare provider Informed of any other medications or supplements you are taking.