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Accurate Education

Nutraceuticals for Central Pain Syndrome Pain (CPSP)

Central Pain Syndrome Pain (CPSP) affects approximately 12% of stroke survivors and is characterized by chronic neuropathic pain—including spontaneous pain, hyperalgesia, and allodynia—corresponding to the injured brain region. Conventional treatments such as gabapentin and other anticonvulsants provide limited effectiveness, and opioids similarly offer incomplete relief.

Neuroinflammation, Mitochondrial Dysfunction and Oxidative Stress

The pathophysiology of CPSP involves excessive neuronal excitability driven by loss of inhibition, while neuroinflammation, mitochondrial dysfunction and oxidative stress also play a role. These mechanisms provide a theoretical rationale for targeting with nutraceuticals representing a promising but unproven adjunctive approach for CPSP.

Melatonin

Melatonin has shown the most direct evidence in CPSP models, with dose-dependent improvements in mechanical allodynia, thermal hyperalgesia, and cold allodynia in animal studies with thalamic lesions. The only available human data on melatonin for neuropathic pain comes from a trial that enrolled patients with various neuropathic pain conditions—*but notably excluded stroke patients*—and found no benefit.

Nutraceuticals

No human trials have evaluated melatonin or other nutraceuticals specifically for central post-stroke pain. Nutraceuticals with preclinical evidence in neuropathic pain include **curcumin**, **resveratrol**, **omega-3 polyunsaturated fatty acids** and astaxanthin which modulate inflammatory signaling pathways while reducing oxidative stress. A systematic review and meta-analysis of animal studies demonstrated that nutraceuticals significantly reduced thermal hyperalgesia and mechanical allodynia/hyperalgesia. These compounds also enhance neuronal survival and reduce hyperexcitability.

Human Studies of Diet and Nutraceuticals in Chronic Neuropathic Pain

However, human evidence is limited and mixed. A systematic review of dietary interventions and supplements for chronic neuropathic pain identified 40 studies, but none specifically addressed CPSP, mostly focusing on neuropathy. The review could not recommend specific supplements for most neuropathic pain conditions due to insufficient evidence, but the following showed promise:

- **Alpha-lipoic acid**
- **Acetyl-L-carnitine**
- **Vitamin D**

Conventional Therapies for Central Pain Syndrome Pain (CPSP)

For CPSP specifically, research has evaluated only conventional pharmacotherapies and neuromodulation techniques.

1. Pharmacotherapies

Conventional pharmacotherapy include :

- amitriptyline (Elavil)
- lamotrigine (Lamictal)
- duloxetine (Cymbalta)
- pregabalin (Lyrica)

The most robust evidence supports amitriptyline and lamotrigine as first-line agents, though response rates are modest. Recent research suggests levetiracetam (Keppra) may be more effective than traditional anticonvulsants, but these findings require validation.

2. Neuromodulation

For CPSP patients refractory to pharmacotherapies, consideration of neuromodulation techniques (repetitive transcranial magnetic stimulation or motor cortex stimulation for severe cases).

• Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS represents the most evidence-based next step when pharmacotherapy is inadequate. though response rates may be lower given the chronicity. Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive brain stimulation technique that uses powerful magnetic pulses to modulate neuronal activity in specific brain regions.

The procedure involves placing an electromagnetic coil on the scalp, which generates a magnetic field that penetrates the skull and induces electrical currents in underlying brain tissue. These currents can alter neuronal excitability and promote beneficial changes in brain function without requiring surgery or anesthesia.

A trial of high-frequency (10-20 Hz) rTMS targeting contralateral to pain (i.e. left hemisphere for right-sided pain) would be reasonable, using protocols of 10 sessions over 2-3 weeks or spaced sessions (e.g., 4 sessions at 3-week intervals). If rTMS provides partial benefit, it may predict response to MCS, as some evidence suggests rTMS response correlates with MCS efficacy.

• Motor Cortex Stimulation (MCS)

Motor cortex stimulation via surgically implanted epidural electrodes yields higher response rates but carries surgical risks. MCS should be reserved for highly refractory cases given surgical risks and lower response rate specifically in post-stroke pain. A 2025 meta-analysis found MCS produced 53.1% mean pain reduction, with 64% of patients experiencing improvement. However, a 2021 double-blind randomized trial demonstrated only 41.4% probability of response, with 39% classified as long-term responders.

Summary

In patients with CRPS failing to respond adequately to conventional pharmacotherapy, given the safety and relative affordability of nutraceuticals, there is a good argument for their trials. It is recommended to start with nutraceuticals directed at neuroinflammation and mitochondrial dysfunction. Based on the ubiquitous nature of systemic inflammation and oxidative stress, a subsequent focus on treating these conditions with nutraceuticals would also be recommended.