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Accurate Education

Nutraceuticals: Agmatine

Agmatine is a natural substance your body already makes in small amounts. Research shows that long-term opioid use depletes the body's natural agmatine — supplementation helps restore what has been lost. Agmatine works by blocking a specific receptor in the spinal cord (called GluN2B) that acts like a "volume knob" for pain — when this receptor is overactive, pain signals get amplified beyond what the actual injury warrants, called "central sensitization," and it's a major driver of chronic pain.

Unlike many prescription medications for pain, such as opioids, gabapentin and duloxetine, agmatine does not cause sedation or cognitive impairment. For patients on opioid medications, agmatine may offer additional benefits: it may make opioids work more effectively (allowing lower doses), it may help prevent Opioid Analgesic Tolerance (OAT - where opioids becomes less effective over time), and may reduce Opioid-Induced Hyperalgesia (OIH - where opioids paradoxically increase pain sensitivity).

2. DIETARY SOURCES

Agmatine is found naturally in fermented foods — wine, beer, sake, miso, soy sauce, and aged cheeses — but the amounts in food are far too low to achieve therapeutic benefits. Supplements are required to reach the doses used in clinical research (1.34–2.67 gm/day). Gut bacteria also produce small amounts of agmatine, which is why probiotics may complement agmatine supplementation.

3. INDICATIONS

- **Lumbar disc-related nerve pain** (radiculopathy)
- **Neuropathic pain** (nerve pain, diabetic neuropathy)
- **Central Sensitization syndromes** (fibromyalgia, chronic widespread pain, nociplastic pain):
- **Opioid Tolerance (OAT)** and **Opioid-Induced Hyperalgesia (OIH)**

4. DOSING

- **Start low** at 500 mg twice a day for the first week, then 1,000 - 1,500 mg twice a day (with food)
- **Dividing into 2 daily doses** with meals to improve tolerability and enhance absorption

5. SENSITIZATION BENEFITS

- **Peripheral Sensitization** (pain sensitivity at the injury site): Agmatine modestly reduces nerve sensitivity at the site of injury through receptor effects on nerve cells.
- **Central Sensitization** (amplified pain processing in the spinal cord): This is agmatine's strongest benefit. It specifically blocks the GluN2B receptor in the spinal cord — the primary driver of pain amplification. Agmatine has no effect on normal, acute pain — it specifically targets abnormal magnified chronic pain.

6. IMPACT ON THE 4 DRIVING FORCES OF CHRONIC PAIN

- **Systemic inflammation** (MODERATE benefit): Reduces inflammatory processing proteins (TNF- α , IL-1 β , IL-6) and suppresses inflammatory pathways (NF- κ B) in tissues.
- **Neuroinflammation** (HIGH benefit). Agmatine enters the brain and spinal cord and shifts immune cells (microglia) from harmful, pro-inflammatory to protective anti-inflammatory states.
- **Oxidative stress** (HIGH benefit): Agmatine activates your body's own antioxidant defense system (the Nrf2 pathway) and directly scavenges damaging free radicals.
- **Mitochondrial dysfunction** (HIGH benefit) Agmatine protects the energy-producing structures in cells (mitochondria), maintaining their function even under inflammatory stress.

7. TIMING, ADMINISTRATION, AND DURATION OF ONSET

- **When to expect results:** Sciatica may show benefits within 14 days. For chronic pain conditions, allow 8–12 weeks for full effect.
- **How long to take it:** One long-term study reported safe daily use for 5 years

8. FORMULATION CONSIDERATIONS

- Use **agmatine sulfate** specifically — this is the only form used in clinical research
- Available as capsules (typically 500–1,000 mg) or bulk powder
- Look for products with $\geq 99\%$ purity and third-party testing (USP, NSF, or ConsumerLab)

9. SYNERGIES WITH OTHER PAIN SUPPLEMENTS AND MEDICATIONS

- **PEA:** Agmatine targets central pain amplification; PEA targets peripheral pain sensitivity — together they cover both ends of the pain pathway. This is the highest-priority combination.
- **Magnesium:** Both work on the same pain receptor (NMDA) but in different, additive ways
- **Curcumin and Omega-3s:** These reduce inflammation in all body tissues while agmatine reduces inflammation mostly in the brain and spinal cord.
- **Opioid medications:** Agmatine enhances opioid pain relief, prevent or reduces tolerance and may counteract opioid-induced pain sensitivity.

10. DRUG INTERACTIONS

- **MAO inhibitor antidepressants** (phenelzine, tranylcypromine, isocarboxazid):
DO NOT COMBINE — Agmatine could interact dangerously with these medications
- **Blood pressure medications:** Agmatine may slightly lower blood pressure
- **Diabetes medications** (insulin, sulfonylureas): Agmatine may enhance their blood sugar-lowering effects — monitor blood sugar more closely when starting
- **L-arginine supplements:** Avoid with high-dose L-arginine, they may work against each other

11. SPECIAL CONSIDERATIONS / TIPS

- **Important note about evidence:** Agmatine has very strong lab and animal studies supporting its use, but human research is still limited (one clinical trial for pain, one 5-year safety report, one small psychiatric study). Its use is recommended based on the best available evidence.
- **Best candidates:** Patients who have been on opioids long-term or whose pain has spread beyond the original injury site or whose pain is magnified out of proportion to the injury



Central
Sensitization



Neuroinflammation



Agmatine



Oxidative
Stress



Mitochondrial
Dysfunction