



Guide to
4 Domains

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B Vitamins

Accurate Education

Nutraceuticals: B Vitamins

B-complex vitamins are a group of eight water-soluble vitamins essential for cellular metabolism, nerve function, and energy production. The "neurotropic" B vitamins—B1 (thiamine), B6 (pyridoxine), B9 (folate), and B12 (cobalamin)—are particularly important for chronic pain management because they regulate inflammatory pathways, protect nerve cells, and support the energy production needed for tissue repair.

In the 4-Domain chronic pain protocol, B-complex supplementation serves as a foundational intervention because these vitamins address all four biological drivers of chronic pain: systemic inflammation, neuroinflammation, oxidative stress, and mitochondrial dysfunction.

(2) THERAPEUTIC BENEFITS (Conditions with moderate to high quality evidence)

1. **Chronic low back pain:** B vitamin complex (B1/B6/B12) combined with NSAIDs achieved $\geq 30\%$ pain reduction in 84% of patients versus 64% with NSAIDs alone in a 2026 randomized trial.
2. **Diabetic peripheral neuropathy:** L-methylfolate/methylcobalamin/pyridoxal-5-phosphate combination (Metanx) produced significant improvement in neuropathy symptom scores and 35% reduction in pain ratings.
3. **Acute musculoskeletal pain:** Meta-analysis found diclofenac + B vitamins reduced treatment duration by approximately 50% compared to diclofenac alone.

(3) "ICEBERG DRUG" CONCEPT

B-complex vitamins exemplify the "iceberg" concept where visible benefits represent only a fraction of total therapeutic value:

Benefits Able to Be Perceived/Measured:

- Pain reduction (up to 30-35% improvement in clinical trials)
- Improved energy levels
- Better response to other pain medications, including NSAIDs

Benefits Not Able to Be Perceived:

- Prevention of neurodegeneration and nerve damage progression
- Reduced risk of central sensitization development
- Homocysteine reduction (cardiovascular and neurological protection)
- Prevention of transition from acute to chronic pain
- Potential reduction in opioid tolerance and opioid-induced hyperalgesia

(4) DIETARY SOURCES

B vitamins are found in various foods, but bioavailability varies significantly:

- **B1 (Thiamine):** Whole grains, pork, legumes (bioavailability ~95% from supplements)
- **B6 (Pyridoxine):** Poultry, fish, potatoes, bananas (bioavailability ~75%)
- **B9 (Folate):** Leafy greens, legumes, fortified grains (natural folate ~50% bioavailable)
- **B12 (Cobalamin):** Animal products only—meat, fish, dairy, eggs (bioavailability decreases with age due to reduced intrinsic factor)

Important: Dietary sources alone are often insufficient for therapeutic benefit in chronic pain.

Multiple medications decrease folate absorption or blood levels, including metformin, methotrexate, sulfasalazine, NSAIDs, and lamotrigine, which may necessitate higher supplementation doses.

(5) IMPACT ON PAIN CONDITIONS

B vitamins directly address underlying pathophysiology in multiple pain conditions:

- **Neuropathic pain:** Methylcobalamin reduces ion channel hyperexcitability in dorsal root ganglion neurons, decreasing pain signal transmission
- **Inflammatory pain:** B vitamins regulate pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β)
- **Musculoskeletal pain:** Support tissue repair through enhanced cellular energy production

(6) IMPACT ON PAIN PROCESSING vs. PAIN CONDITION

B vitamins affect both the underlying condition and pain processing:

- **Pain condition:** Nerve regeneration, myelin repair, reduced tissue inflammation
- **Pain processing:** Modulation of neurotransmitter synthesis (serotonin, dopamine, GABA), reduced neuronal hyperexcitability, decreased central sensitization

(7) BENEFITS FOR PAIN SENSITIZATION

Peripheral Sensitization:

- Methylcobalamin decreases sodium channel activity in peripheral sensory neurons
- B vitamins reduce local inflammatory mediators that sensitize nociceptors
- Support nerve fiber regeneration and restore normal sensory thresholds

Central Sensitization:

- L-methylfolate supports neurotransmitter balance (serotonin, dopamine)
- B12 modulates microglial activation and neuroinflammatory signaling
- Homocysteine reduction decreases excitotoxicity in central pain pathways

(8) BENEFITS FOR TRANSITION OF ACUTE TO CHRONIC PAIN

B vitamins may help reduce the risk of post-op or post-traumatic pain from becoming chronic.

(9) IMPACT ON THE 4 DRIVING FORCES OF CHRONIC PAIN

1. **Systemic Inflammation (SI):** Reduce homocysteine (a pro-inflammatory amino acid); regulate inflammatory cytokine production; support anti-inflammatory pathways
2. **Neuroinflammation (NI):** Modulate microglial cell activation; reduce neuroinflammatory signals (TNF- α , IL-6, IL-1 β); support blood-brain barrier integrity
3. **Oxidative Stress (OS):** Provide antioxidant protection; support glutathione synthesis; counteract endothelial dysfunction and nitrotyrosine accumulation
4. **Mitochondrial Dysfunction (MD):** Serve as essential cofactors for electron transport chain; adenosylcobalamin specifically supports mitochondrial energy metabolism.

(10) SUPPLEMENT FORMULATIONS

1. **Enbrace HR (Rx):** L-methylfolate 7 mg/day: A complete bioactive B-complex + Insurance
2. **Metanx (Rx):** L-methylfolate 3 mg + methylcobalamin 2 mg + PrP 35 mg/day. Tx: DPN
3. **Methylcobalamin sublingual (OTC):** 1–2,mg/day. Bypasses GI absorption
4. **L-methylfolate (Rx or OTC):** 5-15 mg/ day: supplement if MTHFR TT genotype
5. **MTHFR variants:** 30-50% of population affected; L-methylfolate bypasses enzyme deficiency

(11) SYNERGIES

- **NSAIDs:** B vitamins when combined with diclofenac may allow lower NSAID doses
- **Gabapentinoids:** Complementary mechanisms; B vitamins support nerve repair while gabapentinoids modulate calcium channels
- **Opioids:** May reduce opioid-induced hyperalgesia; support neurological function
- **Other Nutraceuticals:** Synergistic with omega-3 fatty acids, magnesium, CoQ10

(13) SPECIAL CONSIDERATIONS - Increased risks of B12 deficiency

- **Monitor** both homocysteine (reflects methylcobalamin pathway) *and* MMA (reflects adenosylcobalamin pathway) for comprehensive B12 status assessment
- **Metformin** users: Increased risk of B12 deficiency; supplementation particularly important
- **Proton pump inhibitor** users: Reduced B12 absorption; sublingual methylcobalamin preferred
- **Elderly patients:** Reduced intrinsic factor and absorption; higher doses may be needed