Supplementation and Nootropics

Steady Practice Applied Science Series — SP-13

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Abstract

The supplementation space is characterized by a large gap between popular claim and scientific evidence, driven by industry funding bias, permissive regulation, and the irrelevant-baseline-population problem (effects measured in deficient or clinical populations are extrapolated to replete healthy adults). This survey adopts a tiered evidence framework. Tier 1 (strong evidence in healthy adults): creatine monohydrate, caffeine, vitamin D in deficiency, omega-3 fatty acids. Tier 2 (moderate evidence with important caveats): magnesium, L-theanine (especially combined with caffeine), ashwagandha, rhodiola rosea. Tier 3 (weak or population-specific evidence): collagen, vitamin C, zinc, melatonin. Tier 4 (popular claims with poor evidence): B vitamins for energy in replete individuals, glutamine, BCAAs for muscle synthesis, most "detox" products. Emerging high-interest compounds — NMN and NR (NAD+ precursors), berberine — are reviewed with honest calibration of the current evidence base, which remains thin for most claims in healthy adults. Supplementation is one of the highest- quality domains for personal science: effects are discrete, timing is controllable, washout is achievable, and some interventions (creatine, caffeine) have large individual variation in response.

Contents

1. The Evidence Problem in Supplementation

The supplementation space is characterized by an unusually wide gap between popular claim and scientific evidence. Contributing factors:

Funding bias: the majority of supplement research is industry-funded, with well-documented publication bias toward positive results (Bjelakovic et al., 2012).

Regulatory arbitrage: supplements are regulated as food, not drugs. They don't require efficacy evidence before sale; they require only safety evidence for removal. Claims can be indirect ("supports energy levels") without clinical validation.

Heterogeneous populations: effects of many supplements are large in deficient populations and near-zero in replete populations. Most research is conducted on deficient or clinical populations, then marketed to the general public.

Mechanistic plausibility $\neq$ clinical efficacy: many supplements have plausible biochemical mechanisms that do not translate to meaningful effects in well-nourished humans.

This survey adopts a calibrated posture: strong evidence gets strong endorsement, weak evidence gets honest "don't know," and the irrelevant baseline population problem is flagged wherever it applies.

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2. Tier 1: Strong Evidence in Healthy Adults

2.1 Creatine Monohydrate

What it is: a naturally occurring compound synthesized from amino acids, stored in muscle as phosphocreatine, and used for rapid ATP regeneration during high-intensity, short-duration effort.

Evidence summary: creatine monohydrate is one of the most-studied performance supplements with an unusually consistent evidence base. A meta-analysis of 22 RCTs found significant improvements in maximal strength (7%), lean body mass (1.4 kg), and high-intensity exercise performance (8%) with creatine supplementation vs. placebo (Lanhers et al., 2017). Effects are robust across study contexts and replication-consistent.

Cognitive effects: emerging evidence for cognitive benefits — particularly in older adults and in tasks under mental fatigue or sleep deprivation. A 2022 meta-analysis (Forbes et al., 2022) found improvements in memory tasks ($d = 0.34$), with larger effects in older adults and high-load cognitive tasks. The mechanism (PCr availability in brain tissue) is plausible.

Dosing: 3–5 g/day maintenance dose is sufficient. Loading (20 g/day $\times$ 5 days) saturates stores faster but produces same steady-state. Creatine monohydrate is equally effective as "enhanced" forms (creatine ethyl ester, Kre-Alkalyn) at lower cost.

Safety: extensively studied; safe for most people at standard doses, including long-term use (10+ years). Not recommended in those with pre-existing kidney disease; evidence of harm in healthy individuals is absent.

Verdict: strongest evidence of any non-pharmaceutical performance supplement. Particularly valuable for strength/power athletes, aging adults (muscle and bone health), and possibly cognitive performance under fatigue.

2.2 Caffeine

(Cross-reference: SP-12 Cognitive Performance for detailed treatment)

Evidence summary: caffeine has the most extensive evidence base of any psychoactive performance enhancer. Aerobic endurance performance: meta-analysis of 21 studies found

average improvement of 3.2% in time-trial performance (Doherty & Smith, 2005). Cognitive performance (sustained attention, alertness): robust effects at 50–400 mg doses (Einöther & Giesbrecht, 2013).

Dosing considerations: tolerance develops within days of daily use, eliminating much of the performance benefit (leaving only withdrawal prevention). Optimal protocol: 3–4 days/week of caffeinated use, or strategic use on high-performance days only. Standard doses 3–6 mg/kg body weight ~60 minutes pre-performance for physical applications.

Genetic variation: CYP1A2 gene substantially influences caffeine metabolism. "Slow metabolizers" (40% of population) may experience performance impairment at doses that benefit fast metabolizers, and have elevated cardiovascular risk from high habitual intake (Cornelis et al., 2006). This is a strong case for N=1 calibration.

Verdict: powerful, well-evidenced, cheap, and legally available. Individual response calibration (dose, timing, frequency) is high-value.

2.3 Vitamin D (in Deficient Individuals)

Evidence summary: Vitamin D deficiency (25-OHD $<$ 50 nmol/L) affects an estimated 40% of North Americans and Europeans (Cashman et al., 2016). In deficient populations, supplementation produces well-documented improvements in: bone density, muscle function, immune function, depression symptoms, and all-cause mortality risk.

In replete individuals: effects of supplementation on outcomes other than bone density are modest to absent. The VITAL trial (Manson et al., 2019) found no reduction in cancer incidence or cardiovascular events with 2,000 IU/day supplementation in already-replete adults, contradicting earlier observational associations.

Dose: 1,000–2,000 IU/day is appropriate for most adults without deficiency. Testing serum 25-OHD and supplementing to correct deficiency (to 75–100 nmol/L) is more targeted than blanket supplementation.

Verdict: highly effective for deficient individuals; marginal for replete individuals. Testing before supplementing is the rational approach.

2.4 Omega-3 Fatty Acids (EPA/DHA)

Evidence summary: omega-3s (particularly EPA and DHA from fish oil or algae) have extensive research across cardiovascular, cognitive, and inflammatory outcomes.

Cardiovascular: the REDUCE-IT trial (Bhatt et al., 2019) found 25% reduction in major cardiovascular events with high-dose EPA (4 g icosapentaenoic acid/day) in high-risk patients. However, this used a pharmaceutical-grade high-dose EPA, not standard fish oil. Standard doses (1–3 g combined EPA+DHA) show more modest effects in primary prevention.

Cognitive/mood: consistent evidence for effect on depression (Sublette et al., 2011; meta-analysis of EPA-predominant formulations: d $\approx$ 0.4). Cognitive effects in healthy adults are modest; better established in aging populations with mild cognitive impairment (Yurko-Mauro et al., 2010).

Inflammatory markers: omega-3s reliably reduce CRP and IL-6 in meta-analyses (Calder, 2013), with clinical significance depending on baseline inflammation.

Dose: for general health, 1–2 g combined EPA+DHA daily. Higher doses for specific therapeutic targets (depression: 2–4 g EPA-predominant).

Verdict: robust evidence for specific populations (high cardiovascular risk, depression, aging-related cognitive decline). Plausible but smaller effects in healthy adults.

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3. Tier 2: Moderate Evidence with Important Caveats

3.1 Magnesium

Context: Magnesium is involved in 300+ enzymatic reactions. Approximately 50% of adults in Western nations have inadequate dietary intake (Nielsen, 2018), and serum magnesium testing underestimates true deficiency (most magnesium is intracellular).

Sleep: magnesium glycinate and magnesium threonate show effects on sleep onset and sleep quality in individuals with low dietary magnesium, but effects in replete individuals are small (Abbasi et al., 2012). The popular "magnesium for sleep" claim is real for deficient people.

Anxiety/stress: modest anxiolytic effects consistent across RCTs, particularly at doses >300 mg/day elemental magnesium (Boyle et al., 2017).

Exercise performance: magnesium depletion during exercise is established; supplementation in athletes with low dietary intake improves performance. In replete athletes, effects are near zero.

Dose: 300–400 mg elemental magnesium/day in divided doses. Glycinate and threonate forms have better bioavailability and fewer GI side effects than oxide.

Verdict: high-value supplement for individuals with likely inadequate intake; modest evidence even then. Diet assessment (leafy greens, nuts, legumes) should precede supplementation.

3.2 L-Theanine (Often Paired with Caffeine)

Evidence summary: L-theanine is an amino acid from green tea with mild anxiolytic and attentional effects. Alone: reliable reduction in subjective anxiety without sedation; modest cognitive effects (Nobre et al., 2008).

With caffeine: the combination is consistently superior to caffeine alone for attention and reaction time, with L-theanine attenuating caffeine-induced anxiety and jitteriness (Giesbrecht et al., 2010; meta-analysis: d $\approx$ 0.4–0.6 for combined vs. placebo on attention). This is one of the few "stacks" with genuine evidence.

Dose: 100–200 mg L-theanine with 50–200 mg caffeine. Standard green tea delivers approximately 30–50 mg per cup of each.

Verdict: well-evidenced as caffeine adjunct for smoothing cognitive stimulant effects. Standalone evidence is more limited.

3.3 Ashwagandha (KSM-66/Sensoril)

Evidence summary: ashwagandha (*Withania somnifera*) is an adaptogen with growing controlled trial evidence. A 2021 systematic review of 12 RCTs found significant reductions in cortisol (d = 0.48), stress/anxiety self-report (d = 0.76), and improvements in sleep quality (d = 0.41) compared to placebo, predominantly using the KSM-66 extract (Pratte et al., 2014; Chandrasekhar et al., 2012; Cheah et al., 2021).

Caveats: most trials are short (8–12 weeks), conducted in mildly stressed adults, and industry-adjacent. Independent replication is growing but not extensive. Effect sizes are moderate and consistent enough to take seriously.

Physical performance: 5% improvement in VO2max and significant strength gains vs. placebo in two RCTs in healthy adults (Wankhede et al., 2015; Sandhu et al., 2010). Mechanism possibly through cortisol reduction and anabolic hormone support.

Safety: generally well-tolerated; rare case reports of liver injury with very high doses or specific preparations. Standard doses (300–600 mg standardized extract) have acceptable safety profile.

Verdict: better evidence than most adaptogens; modest real effects on stress markers and possibly performance. The stress/sleep evidence is most consistent.

3.4 Rhodiola Rosea

Evidence summary: another adaptogen with a reasonable evidence base for reducing fatigue and mental performance under stress. A 2012 meta-analysis of 11 RCTs found significant effects on physical and mental fatigue (Hung et al., 2011), though study quality varied.

Cognitive performance under fatigue: most consistent finding. In sleep-deprived or highly stressed subjects, rhodiola (SHR-5 extract) reduces fatigue and improves performance on cognitive tasks (Shevtsov et al., 2003; Darbinyan et al., 2000). Effects in well-rested, low-stress subjects are much smaller.

Dose: 200–400 mg standardized extract (SHR-5 form, 3% rosavins, 1% salidrosides) taken in the morning (can interfere with sleep if taken late).

Verdict: plausible for cognitively demanding periods or during high-stress/low-sleep episodes. Less useful as a daily supplement without those conditions.

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4. Tier 3: Weak Evidence or Population-Specific

4.1 Collagen / Collagen Peptides

Evidence summary: collagen peptides (especially type I hydrolyzed collagen with vitamin C) show emerging evidence for joint health — modest improvements in joint pain and mobility in athletes with knee osteoarthritis (Shaw et al., 2017). Evidence for skin elasticity improvements is more consistent but requires 2.5–10 g/day over 8+ weeks.

Muscle protein synthesis: collagen is an incomplete protein (lacks adequate leucine for muscle protein synthesis). It is not equivalent to whey or casein for muscle building; evidence suggests it can improve connective tissue synthesis when combined with appropriate exercise loading.

Verdict: reasonable evidence for joint health and skin applications; not useful as a protein source for muscle building.

4.2 Vitamin C

Evidence summary: vitamin C is essential; true deficiency causes scurvy. In replete adults with adequate dietary intake ($>$ 90 mg/day from food), additional supplementation shows no reliable benefits for immune function, cardiovascular outcomes, or mortality (Bjelakovic et al., 2012 Cochrane review).

Upper respiratory illness: high-dose vitamin C (1–2 g/day) reduces duration of common cold by approximately 8% in the general population — a modest but real effect (Hemilä & Chalker, 2013). Not effective for prevention in the general population; possibly effective for prevention in individuals under extreme physical stress (marathoners, military recruits).

Verdict: ensure adequate dietary intake; supplementation unlikely to add meaningful benefit in replete adults outside of extreme physical stress contexts.

4.3 Zinc

Evidence summary: zinc deficiency (more common than expected — affecting 10–15% of Western adults, particularly vegetarians and elderly) impairs immune function and wound

healing with well-documented effects. Correction of deficiency rapidly restores function.

Cold treatment: zinc lozenges started within 24 hours of symptom onset reduce cold duration by approximately 33% (Hemilä, 2011). This is a real effect with reasonable evidence but requires high-dose zinc acetate/gluconate lozenges (>75 mg elemental zinc/day) — not standard zinc supplements.

Verdict: targeted use for deficiency correction and acute cold treatment; daily supplementation in replete individuals has minimal evidence.

4.4 Melatonin

Evidence summary: exogenous melatonin is primarily a circadian timing signal, not a sleep-promoting drug per se. At physiologically relevant doses (0.5–1 mg), it advances or delays the circadian phase — useful for jet lag and shift work. At higher doses (5–10 mg), it also has mild sedative effects but with disrupted sleep architecture and daytime grogginess risks.

Jet lag: strong evidence for melatonin 0.5–5 mg taken at destination bedtime for east-ward travel jet lag (Herxheimer & Petrie, 2002 Cochrane review).

Sleep latency in shift workers: moderate evidence for reducing sleep onset difficulty when sleep schedule is misaligned with circadian phase.

Chronic use for primary insomnia: small effects (Buscemi et al., 2005 meta-analysis; d $\approx$ 0.19 for sleep latency). Not a substitute for CBT-I.

Verdict: appropriate for jet lag and circadian shift adjustment; marginally useful for sleep onset in circadian-misaligned individuals; limited evidence for general sleep improvement. Low dose (0.5–1 mg) is as effective as high dose and avoids receptor downregulation.

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5. Tier 4: Popular Claims with Poor Evidence

5.1 B Vitamins for Energy

Status: B vitamins are cofactors in energy metabolism — but supplementation in non-deficient individuals does not increase energy production. This is one of the most reliably marketed

but scientifically unfounded supplement claims. Energy drinks and "B-complex for energy" products capitalize on the metabolic role while providing no benefit to replete users (Kennedy, 2016).

Exception: B12 deficiency is common in vegans, vegetarians, and elderly individuals. Correction produces real energy and neurological benefits.

5.2 Glutamine for Immune Support

Status: glutamine supplements are marketed for immune function in athletes. Evidence in severely ill or post-surgical patients is positive; evidence in healthy athletes doing recreational exercise is essentially absent (Antonio & Street, 1999).

5.3 Branched-Chain Amino Acids (BCAAs) for Muscle

Status: BCAAs trigger muscle protein synthesis signaling but do not provide sufficient essential amino acid content for meaningful MPS. Whey protein (containing all essential amino acids) consistently outperforms BCAAs for muscle protein synthesis in controlled comparisons (Wolfe, 2017). BCAAs are an expensive way to get a fraction of the benefit of complete protein.

5.4 Most "Detox" and "Cleanse" Products

Status: the liver and kidneys perform continuous endogenous detoxification. No commercial "detox" product has demonstrated superior toxin removal compared to normal hepatic/renal function in healthy individuals. These are marketing constructs without mechanistic plausibility or clinical evidence.

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6. Emerging and High-Interest Compounds

These compounds attract significant commercial and research attention. Evidence is early; claims routinely outrun data.

6.1 NMN and NR (NAD+ Precursors)

Nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) are precursors to NAD+, a coenzyme central to cellular energy metabolism. NAD+ levels decline with age, and animal studies — predominantly in rodents — show NAD+ repletion via NMN/NR reverses several age-related physiological declines (muscle function, metabolic health, mitochondrial biogenesis). The rodent evidence has generated enormous popular interest.

Human evidence: sparse and preliminary. At the time of writing, fewer than 15 placebo-controlled human trials exist, most with small samples ($N < 50$) and short durations (8–12 weeks). Mills et al. (2016, *Cell Metabolism*): first human NMN study (N=10, open-label) showed safety and increased muscle NAD+ levels. Subsequent double-blind RCTs have shown NR increases blood NAD+ metabolites consistently, but functional outcomes (exercise capacity, metabolic markers, cognitive performance) are mixed, with most studies failing to show significant improvement in primary endpoints in healthy adults (Martens et al., 2018; Dollerup et al., 2018).

Key caveats: the bioavailability and tissue distribution of oral NMN vs. NR differ and remain debated. Blood NAD+ levels increasing does not establish that intracellular NAD+ in target tissues (muscle, brain) increases meaningfully. The animal-to-human translation is uncertain. Most positive human findings are in older adults with metabolic disease, not healthy younger adults.

Verdict: mechanistically plausible, insufficient human RCT evidence for efficacy claims in healthy adults. An intellectually honest Tier 3 at best — potentially interesting, currently unproven at the outcome level. Worth watching; not worth confident recommendation.

6.2 Berberine

Berberine is an alkaloid found in several plants (barberry, goldenseal) with multiple metabolic mechanisms of action, primarily through AMPK activation — the same pathway activated by metformin and exercise.

Evidence: berberine has more human RCT evidence than most natural compounds. A 2012 meta-analysis of 27 RCTs found significant reductions in fasting blood glucose (-0.90 mmol/L), HbA1c (-0.71%), LDL cholesterol (-0.49 mmol/L), and triglycerides vs. placebo (Dong et al.,

2012). Effects appear clinically comparable to metformin in type 2 diabetes management in several direct comparisons.

For healthy adults: effects in non-diabetic individuals with normal glucose are much smaller — the baseline-population problem again. Berberine's glucose-lowering effects are largest when there is glucose dysregulation to correct. Gut microbiome modulation (berberine alters microbial composition) may produce secondary effects but the clinical relevance in healthy adults is unclear.

Safety note: berberine inhibits CYP3A4 and P-glycoprotein, creating drug interaction potential. Not appropriate without medical review in individuals on medications.

Verdict: strong evidence in metabolic disease; modest expected benefit in healthy adults without glucose dysregulation. Better positioned as a Tier 2 compound for the specific context of improving metabolic markers than as a general health supplement.

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7. The Personal Experimentation Case

The most compelling use case for a self-tracking platform in the supplementation domain is structured N=1 experimentation (see SP-9 for methodology). For supplements where: 1. Individual response is high (caffeine metabolism, vitamin D baseline, magnesium intake) 2. Subjective outcomes are tractable (energy, focus, sleep quality) 3. The effect may be real but size is uncertain

…crossover N=1 experiments provide genuine personal evidence that population averages cannot.

A practical N=1 supplement trial: - **Duration**: 4–6 weeks per arm (washout $\geq$ 2 weeks) - **Blinded condition**: user doesn't know which week is active vs. placebo (requires third-party blinding or identical capsules) - **Outcomes**: daily subjective ratings on sleep quality, energy, focus; wearable HRV/sleep data - **Analysis**: paired t-test or Bayesian within-person comparison

Caffeine dose calibration, magnesium's effect on personal sleep quality, and ashwagandha's effect on stress perception are all tractable personal experiments with low safety risk and high individual variability.

8. Platform Design Principles

Default to evidence tiers: clearly communicate where each supplement sits on the evidence gradient; resist the temptation to present weak evidence as promising

Surface the "deficiency first" question: before suggesting any micronutrient supplement, prompt users to assess baseline dietary intake or serum levels where relevant (vitamin D, zinc, magnesium, B12)

Caffeine calibration as a first experiment: caffeine protocol optimization is the highest expected-value starting point for most users — large effects, cheap to test, individual variation in optimal dose/timing/frequency is real

Support structured N=1 trials: build supplement logging with blinding protocols and analysis built in; give users a framework to generate personal evidence

Avoid monetizing supplement partnerships: recommending supplements based on affiliate revenue severely compromises user trust and scientific credibility; platform credibility is a more valuable long-term asset

Track context with supplement use: time of day, food state, sleep on previous night, exercise — supplement effects are highly context-dependent and personal logs without these covariates are largely uninterpretable

9. Individual Variation

Supplement response varies more between individuals than population-average effect sizes suggest. For several high-interest supplements, genetic, physiological, and dietary factors predict who responds and who does not — making personal N=1 experimentation more informative than population averages for individual decision-making.

MTHFR variants determine folate supplement form efficacy. The MTHFR C677T polymorphism, present in approximately 10% of the population in homozygous form and 40% in heterozygous form, reduces the enzyme's efficiency in converting dietary and supplemental

folic acid to the active form (5-methyltetrahydrofolate) used in cellular methylation reactions. Homozygous carriers show 70% reduction in enzyme activity (Frosst et al., 1995). For these individuals, standard folic acid supplementation is substantially less bioavailable; they require direct methylfolate (5-MTHF) to achieve equivalent serum folate levels. This is one of the clearest documented cases where the same supplement is effectively inert for one genetic subgroup and functional for another based on a single SNP — a model for thinking about pharmacogenomic variation more broadly.

Creatine non-responders represent 25–30% of supplementing populations. Approximately one in four individuals shows minimal or no measurable response to standard creatine supplementation (3–5 g/day for 4+ weeks) in either strength or cognitive outcomes. Non-responders tend to have higher baseline muscle phosphocreatine stores, meaning supplementation produces no meaningful increase in the saturation that drives performance effects. Vegetarians and vegans — who consume little to no dietary creatine — show the largest and most reliable response to supplementation because they are starting from lower baseline saturation. Omnivores with high dietary meat intake are more likely to be partial or full non-responders (Greenhaff et al., 1994). Baseline creatine status, not supplementation dose, primarily determines effect size.

Vitamin D serum response to oral supplementation varies 4–6 fold. The same oral dose of vitamin D3 (e.g., 2000 IU/day) produces a 4–6 fold range of serum 25(OH)D response across individuals, driven by: gut absorption efficiency (influenced by VDR gene variants), adipose tissue sequestration (D3 is fat-soluble; individuals with higher body fat percentage store more, reducing circulating levels per dose), baseline sun exposure, and baseline serum level. Cashman et al. (2016) documented this response variance in a large European population study. The clinical implication is direct: supplementing a fixed dose and assuming adequate status is unreliable. The only calibration method is measuring serum 25(OH)D before supplementation (establishing baseline and deficiency status) and re-measuring after 8–12 weeks of supplementation to verify adequate response. "I'm taking 2000 IU" is not equivalent to "I have adequate vitamin D status."

Caffeine non-response results from the joint effect of CYP1A2 metabolism rate and ADORA2A receptor sensitivity. CYP1A2 determines how quickly caffeine is cleared; ADORA2A determines how sensitive adenosine receptors are to caffeine's competitive blocking action. Fast metabolizers (CYP1A2 *1F*/1F genotype) clear caffeine before it has extended its

adenosine-blocking effect to a cognitively meaningful duration. Simultaneously, individuals with low-sensitivity ADORA2A variants experience less receptor-level effect per unit caffeine. The combination — fast metabolism plus low receptor sensitivity — produces functional caffeine non-response: the compound is metabolized before accumulating sufficient adenosine-blocking activity to measurably improve cognitive performance. Cornelis et al. (2006) demonstrated these combined pharmacogenomic effects in a population study. This explains why a meaningful fraction of the population self-reports minimal cognitive benefit from caffeine, consistent with the underlying pharmacogenomics.

Practical self-experiment implication. For any supplement you believe may be working, run a formal 4-week on/4-week off crossover before concluding it is effective. The critical design feature is measuring your target outcome (sleep score, energy rating, focus rating, strength) with the same instrument throughout both conditions. Placebo response rates in supplement studies routinely reach 30–40% (Beecher, 1955), meaning subjective improvement during the active phase is insufficient evidence — the critical comparison is to your own control phase. Pre-specify your decision threshold before seeing the results: "I will continue this supplement if my average score during the active phase exceeds my control phase average by at least 0.5 points on a 10-point scale." Without pre-specification, threshold rationalization after seeing results is nearly universal.

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10. N=1 Experiment Protocols

These protocols are designed for individual self-experimentation. Each uses a within-person design to generate personalized evidence that population averages cannot provide.

Creatine N=1 crossover (8 weeks). 5g monohydrate daily for 4 weeks, then 4-week washout. Measure: weekly working memory test score (digit span or dual n-back), training performance (if applicable), and daily energy rating. Decision: $\geq$10% working memory improvement sustained to week 4 = cognitive responder; keep if training volume is high or diet is low-meat.

Magnesium glycinate sleep experiment (4 weeks). 200–400mg glycinate form 1 hour before bed for 2 weeks, then 2-week washout. Measure: sleep onset time, HRV, and morning energy rating. Decision: $\geq$15-minute reduction in sleep onset time or $\geq$5% HRV improvement

= responder. Note: run this during a stable life period — travel or high stress confounds the result.

Vitamin D titration (12 weeks). Get serum 25(OH)D baseline. Supplement at 2000 IU/day for 6 weeks, then 4000 IU/day for 6 weeks. Retest serum at weeks 6 and 12. Target: 40–60 ng/mL. Adjust dose to hit target. Track energy and mood ratings throughout — improvement signals deficiency correction. Decision: dose producing target serum level with stable energy = your maintenance dose.

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11. Conclusion

The supplementation landscape rewards calibration and skepticism in equal measure. A handful of supplements have robust evidence with meaningful effect sizes for relevant populations: creatine for performance and possibly cognitive fatigue, caffeine for performance and attention, vitamin D and omega-3s for specific deficiency and risk contexts, and a small set of adaptogens (ashwagandha, rhodiola) with increasingly solid evidence for stress and fatigue applications.

The majority of the supplement market operates in the space between plausible mechanism and absent clinical evidence, targeting populations who are already replete in the nutrient being sold. The right response is not blanket skepticism or blanket acceptance — it's demand for the specific evidence type: what population, what outcome, what dose, and does it replicate?

Where individual response variation is high, personal experimentation with appropriate methodology can yield better guidance than population averages.

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