Dietary Supplements

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Disclosures

I have no financial disclosures to report

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Objectives

- Review current literature on use of creatine, including cautions and evaluation of kidney function
- Discuss recently reclassified peptides and review considerations and cautions for use
- Discuss clinical concerns with kratom and 7-OH use
- Review high dose nicotine use and associated clinical concerns

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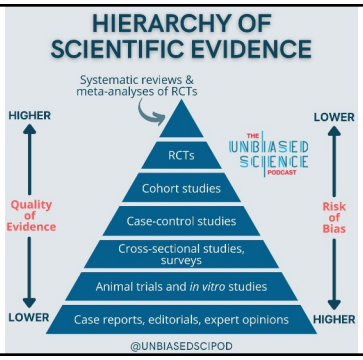

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Creatine

Creatine is an endogenous compound synthesized from arginine, glycine and methionine. This dietary supplement can be acquired from food sources such as meat and fish, along with athlete supplement powders. The majority is stored in skeletal muscle.

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Creatine

Established benefits (2025 meta analysis):

- Muscle strength - greater gain in untrained individuals
- Low dose supplementation of 0.1 g/kg body weight combined with high intensity exercise yields optimal results [Example - 150 pounds → 68 kg → 6.8 grams max dose]
- Improved high intensity exercise performance, enhanced recovery, greater training adaptation

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Creatine

Emerging evidence (2023 meta analysis, 2024 European Food Safety Authority review, 2025 systematic review):

- Can increase brain creatine stores
- Improved memory performance most significant in older adults (66-76 years old), minimal effects in younger adults
- Cognitive benefits are most pronounced during metabolic stress such as sleep deprivation
- Cause and effect is not established, inconsistent effects across studies
- 5 of 6 studies reported a positive relationship between creatine and cognition, but most had fair to poor methodological quality

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Creatine

Additional possible clinical applications:

- Vegetarians and vegans - since they do not consume dietary creatine, supplementation is effective in increasing muscular and neuropsychological performance
- Studies in neurodegenerative diseases such as Parkinson's disease, traumatic brain injury, concussion, diabetes - no clear outcomes yet
- Statin myopathy - small pilot study in 2024 showed reduction of symptoms but not reduction of CK levels in early stage of symptoms at 1 gram TID dosing

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Creatine

Creatine use in mental health:

- Treatment resistant depression in women - small double blind placebo controlled trial in 2012 showed modest evidence support use as an adjunctive treatment to SSRI at 5 gram/day dose
- 2025 meta analysis of 11 studies showed small effect size (2.2 point increase on HAM-D scale, 3 points is considered clinically significant), study quality was generally low
- Caution with patients with bipolar spectrum disorders - 2026 study from Canada found that 2 of 17 patients developed mania

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Creatine

- **Recommended daily dose for healthy adults is 3-5 grams per day**
- Intake of 3 grams per day is unlikely to pose safety concerns in healthy adults EXCLUDING pregnant and breastfeeding women
- Daily turnover rate in your muscles is 2.5-3 grams/day, so this is an appropriate dose for healthy adults doing recreational exercise
- High intensity training may use up to 5-6 grams per day, but after loading phase, muscle creatine stores can be maintained with as little as 2 grams/day
- Studies demonstrate safety with doses up to 30 grams/day for up to 5 years, but doses above 6 grams should be prescribed for specific conditions

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Creatine and Kidney Function

- **Creatine supplementation does not impair kidney function in healthy individuals,** despite causing a modest increase in serum creatinine levels. The elevated creatinine reflects increased creatine metabolism rather than renal dysfunction, and glomerular filtration rate (GFR) remains unchanged.
- 2025 meta-analysis found that creatine was associated with small but statistically significant transient increase in serum creatinine (0.07 µmol/L)
- Long term studies for up to 5 years have demonstrated no detrimental effects on kidney function in healthy adults
- **Important caveats:** Individuals with pre-existing renal disease, diabetes, hypertension, or reduced GFR should avoid high-dose creatine supplementation (>3-5 g/day) due to theoretical concerns about increased metabolic load on compromised kidneys due to limited data on safety

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Comp. Metabolic Panel (14)

Glucose	84	76	87	86
BUN	13	13	10	14
Creatinine	**1.38 H**	0.77	0.75	0.76
eGFR	**54 L**	110	114	113
BUN/Creatinine Ratio	9	17	13	18
Sodium	139	138	138	138
Potassium	4.4	4.6	4.7	4.1
Chloride	101	102	103	104
Carbon Dioxide, Total	**18 L**	21	23	25
Calcium	9.8	9.2	9.2	9.2
Protein, Total	7.2	6.6	6.6	6.7
Albumin	4.9	4.8	4.6	4.5
Globulin, Total	2.3	1.8	2.0	2.2
Bilirubin, Total	0.4	0.6	0.2	0.5
Alkaline Phosphatase	47	49	59	55
AST (SGOT)	27	18	13	15
ALT (SGPT)	28	12	10	9

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Creatine and Kidney Function

- **Creatine supplementation transiently increases creatinine production through non-renal pathways, leading to falsely elevated serum creatinine and spuriously low calculated eGFR despite normal kidney function**
- **Cystatin C-based** is not affected by muscle mass, diet, or creatine supplementation (Cash cost for this lab is about $160 vs CMP for about $7)
- **Urine albumin-to-creatinine ratio:** Should remain normal in creatine-induced creatinine elevation
- **Blood urea nitrogen (BUN):** Typically unchanged with creatine supplementation alone

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Peptides

Peptides are chemical messengers in the form of short chains of amino acids – think of them like text messages that go to organs to tell them to do a particular task.

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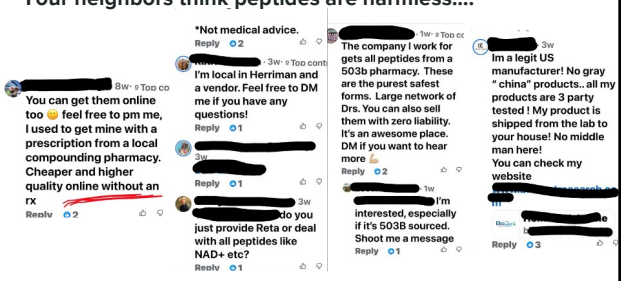
Your neighbors think peptides are harmless....



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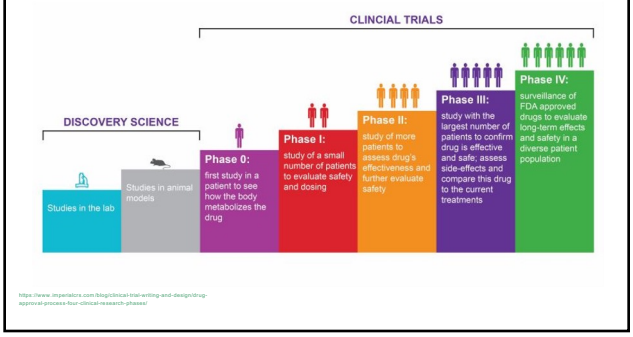

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Peptides background

- Examples of endogenous peptides include endorphins such as dopamine, oxytocin, leptin, ghrelin, GLP-1, and insulin
- They can be released from organ to signal another organ, or cell to cell
- They are short lived and degrade quickly after delivering their message
- Peptide drugs are a "medium size" drug that typically need to be injected
- Peptide drugs mimic actions of hormones or extend/block duration of natural signal
- Peptide drugs are formulated to last longer in the body (Example - GLP-1 naturally occurring breaks down in minutes, GLP-1 agonists last days)
- Peptide is a chemistry term, not a proof of efficacy term

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Peptide reclassification

- September 2023 - Biden administration identified peptides that had potential for significant safety risks and designated them to Category 2 that prohibited compounding
- Category 1 - Bulk drug substances under evaluation
- Cagetory 2 - Bulk drug substances that raise significant safety concerns
- Category 3 - Bulk drug substances nominated without adequate support
- Announcement in April 2026 of intent to move 12 of these peptides back to Category 1 without any scientific evidence of safety or efficacy
- Meetings will be held in late July 2026 to discuss these 12 peptides

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Peptides on track to be reclassified

- BPC 157
- Cathelicidin LL-37
- Dihexa Acetate
- Emideltide (DSIP)
- GHK-Cu
- KPV
- Mechano-Growth Factor, Pegylated
- Melanotan II
- MOTs-C
- Semax (heptapeptide)
- Thymosin Beta-4, Fragment

- **"Libertarian approach to medicine" - patient assumes the risk**
- These are often purchased on the "gray market" as research grade ingredients
- Many pharmacies compound these and make claims that are not evidence based
- Formulations are being sold that have no data to back them up - nasal spray, patches, oral, injections
- Biologically active = real risk for harm!

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BPC-157

- Synthetic form of body protective compound 157 that naturally occurs in gastric juices
- **Mechanism:** Promotes tissue regeneration through angiogenesis, fibroblast activity, and nitric oxide signaling
- Almost all existing data on this compound comes from a single group of researchers in Croatia
- **Data** is based on rodent studies - only published human data is retrospective data on 12 patients (7 reported knee pain relief), and a pilot study of 2 patients
- **Concern that stimulation of new blood vessels could potentially accelerate cancer growth**

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Ipamorelin

- **Mechanism:** Ghrelin receptor agonist that stimulates the release of growth hormone (GH)
- **Marketing claims:** improve metabolism and sleep, enhance sex drive, reduce wrinkles, reduce body fat and increase muscle mass without diet or exercise
- Often combined with BPC-157 ("peptide stacking")
- **Data:** Rodent data actually showed an increase in body weight and fat following injections
- **Human data** - most significant study published in 2014 was investigating use for postoperative ileus, and it was no more effective than placebo
- No human clinical trials in the last decade

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CJC-1295

- **Mechanism:** Analogue of growth hormone releasing hormone that stimulates release of GH and secretion of IGF-1
- **Marketing claims:** Increase muscle mass, decrease body fat, improve sleep, boost mood
- **Data:** body composition changes were demonstrated in rats that were genetically modified to not have the gene for growth hormone releasing hormone
- **Human data** is limited to a trial in 2006 showing that a single injection of CJC-1295 can increase GH and IGF-1 for 6 and 9 days prospectively
- Trials were investigating treatment for lipodystrophy in HIV patients, discontinued when a trial participant died from a heart attack

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Melanotan II

- **Mechanism:** Melanotan II is an variant of melanotan I (afamelanotide), which has legitimate use for erythropoietic protoporphyria
- **Marketing:** Known as the "Barbie drug", this is a synthetic analogue of alpha melanocyte stimulating hormone that non-selectively stimulates melanogenesis to facilitate self tanning
- Additional effects include appetite suppression and stimulation of erections
- Side effects include nausea, vomiting, facial flushing, priapism
- **Significant concern** that stimulation of melanocytes can cause skin complications, including melanoma, as well as risk for rhabdomyolysis and encephalopathy

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Thymosin Beta-4 fragment

- **Mechanism:** Cellular constituent in many tissues that regulates actin polymerization → cell proliferation, migration, and differentiation, and a general role in tissue regeneration
- **Data:** Animal studies and cell cultures of the full 43 amino acid chain show migration of cells, formation of blood vessels, maturation of stem cells, and lowering of inflammatory cytokines
- Phase 2 clinical trials of the full thymosin beta 4 peptide have shown improvement in pressure ulcers, epidermolysis bullosa, and dry eye
- Full chain is considered to be a performance enhancing substance, and is banned in sports
- **Concern:** Synthetic form can be several molecules that are shorter fragments, including TB-500, Ac-SDKP. - No human clinical trials have been published

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Beware the marketing hype

- **We have ZERO strong clinical evidence to support use of these unregulated peptides by themselves or as "peptide stacks"**
- We do not know what cellular targets these peptides stimulate and therefore do not have good characterization of either benefits or risks
- Peptides can be unstable and clump together, increasing risk for immunogenic reaction particularly when combined
- We do not know how to dose or administer these medications safely
- Gray market purchases are very dangerous - unknown sources and contaminants
- **Rat data ≠ Human data**

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Kratom

Also known as "gas station heroin", this herb has both stimulant and opioid effects. More than 200 Utahns have died between 2018 and early 2026 from kratom overdoses.

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Kratom - Substance of Abuse or Therapeutic Plant?

Kratom products vary significantly in form and packaging.

https://coast.venturacounty.gov/prescribers-care/kratom

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Kratom - Background

"Kratom" refers to both *Mitragyna speciosa,* a tree native to Southeast Asia, and to products derived from its leaves that are marketed as herbal supplements to be ingested as tea or capsules, or smoked

Kratom has been used in Southeast Asia for hundreds of years in whole leaf form

Mechanism of action is based on two psychoactive alkaloids: Mitragynine and it's metabolite, 7-hydroxymitragynine (7-OH)

Products in the united states often have higher levels of 7-OH, which is significantly more potent than whole leaf and therefore more potential for harm

Research is ongoing, but so far, kratom has not been demonstrated to be safe or effective for medical conditions

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Kratom - Legal Status

- Kratom is banned for sale in several countries
- U.S. DEA has labeled it as a drug of concern, but it is not classified as a controlled substance
- Effective May 6, 2026, Utah law enacted the following safeguards (SB45):
  - Ban on sale of enhanced/synthetic products, including those with high 7-OH at all retailers
  - Only validated whole leaf product may be sold, and only in licensed smoke shops or specialty shops, to persons 21 years of age or older
  - Kratom processors and retailers have to be registered with the Utah Department of Agriculture and Food
  - Manufacturers have until May 6, 2027 to stop producing enhanced products in the state

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Kratom - Mechanism of Action

- Partial agonist for Mu-opioid receptors
  - Biased signaling on G proteins produces analgesia with lower risk of constipation and respiratory depression than traditional opioids in whole leaf, 3x higher risk for 7-OH
- Competitive antagonism of Kappa- and Delta-Opioid receptor activity
  - Pain relief, and potentially reduced risk for dependence
- Adrenergic alpha-2 receptors
  - Associated with hypothermia and antinociceptive properties (pain relief)
- Serotonergic receptors
  - Associated with mood elevation and anxiety relief
- Dopaminergic receptors
  - May contribute to stimulant and euphoric properties
- Neuronal calcium channel receptors
  - Modulation may contribute to analgesia and other CNS effects

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Kratom - Effects

- **Low doses have stimulant like effects** - increased energy, alertness
- **High doses have more opioid effects** - analgesia, sedation, euphoria
- **Significant CYP450 interactions** -Inhibits CYP2D6 and CYP3A4, may effect P-glycoprotein and UGT enzymes,
- **Potential side effects**
  - **Mild** - constipation, drowsiness, dizziness, itching, sweating, dry mouth, increased urination, appetite suppression, insomnia, muscle pain
  - **Serious** - confusion, psychosis, hallucinations, seizures, hypertension, respiratory depression, vomiting, liver problems, dependence, death
  - **Risk for significant withdrawal symptoms** - 7-OH is far more potent than morphine
- Significant concern for contamination and variation in dose - enhanced products may have up to 500% more 7-OH than whole leaf

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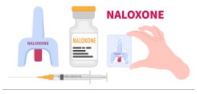
Kratom Overdose Treatment

- **Acute overdose with respiratory depression is treated with naloxone**
- Utahnaloxone.org - resources for free kits at fire stations and libraries around the state, administration instructions, and prescriber resources. Kits can also be purchased at any pharmacy without a prescription.
- There is no established treatment for withdrawal, but buprenorphine may be considered



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Nicotine

There is a shift in method of nicotine delivery to smokeless products, but it still carries many risks. “There are no safe nicotine products, including nicotine pouches.” (CDC)

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Nicotine - Constantly Evolving to Maximize Addiction

- **Nicotine is as or more addictive as hard drugs**
- 30% transition rate from first use to dependence
- ⅔ of smokers want to quit at any time
- ⅓ try to quit
- 2% are successful
- Last year, nearly 795 million cans of Zyn were sold, double from 2023

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Nicotine forms

- **Cigarettes/Cigars/Pipe** - Inhaled nicotine hits the brain in 7-10 seconds, is brief, and reinforces addiction. Additives to maximize nicotine delivery.
- **Vapes** - High variability in potency, formulated to appeal to teens. Multiple additional toxic chemicals. *May* have greater success using vapes for cessation than lozenges, patches, or gums.
- **Chew** - Single container = 80 cigarettes. High risk of oral, esophageal and pancreatic cancers, in addition to periodontal disease.
- **Pouches** - Wide range of doses (1.5-30 mg, common 2-12 mg). Higher doses are akin to smoking several cigarettes at once. Same cancer risk as chew.
- **Patches** - Dose strengths of 21 mg, 14 mg, 7 mg. 21 mg roughly = 1 pack per day of cigarettes. Very heavy smokers may need 42 mg.
- **Lozenges/Gum** - 2 and 4 mg strengths, maximum 24 doses/day.

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Nicotine - Mechanism of Action

- Nicotine → **agonist at nicotinic acetylcholine receptors (nAChRs)**, which are ligand-gated ion channels normally activated by the endogenous neurotransmitter acetylcholine
- The **α4β2 nAChR subtype** is the primary target in the brain mediating nicotine's addictive properties → enhances the firing rate and phasic burst firing of dopamine neurons in the **ventral tegmental area (VTA)**, activating the **mesolimbic dopamine system** and triggering dopamine release in the nucleus accumbens — the brain's reward center

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Nicotine - Mechanism of Action

Beyond dopamine, nicotine stimulates the release of multiple neurotransmitters:

- **Glutamate** — facilitates further dopamine release
- **GABA** — inhibits dopamine release (but becomes desensitized with chronic use, shifting the balance toward excitation)
- **Norepinephrine** — contributes to arousal and cognitive enhancement
- **Serotonin, β-endorphin, acetylcholine, vasopressin** — contribute to mood modulation, analgesia, and other effects

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Nicotine - Physical Effects

- **Increased heart rate, blood pressure, and cardiac contractility**, with hemodynamic effects peaking within 5–10 minutes of exposure
- **Peripheral vasoconstriction** → elevated blood pressure
- **Increased arterial stiffness** and **impaired endothelial function**
- **Platelet activation** and prothrombotic state
- **Proarrhythmic effects** - Long-term usemay promote cardiac remodeling and fibrosis
- **Lipolysis and insulin resistance**, increasing the risk of type 2 diabetes
- **Decreases HDL** and increases atherogenicity
- **Substantially higher risk for delayed wound healing and infection**
- **Lungs** - increase permeability of membrane, impaired barrier function
- **Disruptions in brain development** in child/teen use
- **Pregnancy** - low birth weight, premature birth, premature rupture of membranes, increased risk for cleft palate, ectopic pregnancy, placenta previa, impaired neurodevelopment
- **Tumor promoting properties**, though it has not been classified as a complete carcinogen

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Nicotine - Withdrawal

Nicotine withdrawal is characterized by a well-defined constellation of symptoms that typically **begin within a few hours of the last tobacco use, peak at 2–3 days, and largely subside over 2–4 weeks, though cravings may persist for months.**

- Irritability, frustration, or anger
- Anxiety
- Depressed mood / dysphoria
- Difficulty concentrating
- Restlessness
- Insomnia
- Increased appetite / weight gain
- Cravings for tobacco

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Nicotine - Off-label Uses and ”Influencer Marketing”

- **Nicotine - miracle cure that “they” don’t want you to know about?**
- Multiple influencers have posted about use, typically with patches or pouches, with numerous claims that are unsupported by data, most coming from a chiropractor named Bryan Ardis
- Claims include cures for autism, Parkinson’s disease, Alzheimer’s, ulcerative colitis, multiple sclerosis, protection from COVID, and more
- Research has shown no improvement in either Alzheimer’s or Parkinson’s disease progression
- Mild improvement in ulcerative colitis with nicotine enemas, but no better than current treatments
- No evidence that nicotine improves autism, and side effects are significant

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Nicotine Cessation Resources

- waytoquit.org
  - Nicotine replacement (patches and lozenges) and cessation medications
  - Customized quitting plan
  - Five personal coaching sessions
  - Online community
  - Text and email support
  - Quitstart app
  - Use the 5 D’s – delay, distract, drink water, deep breaths, and discuss
  - **All services are free and you can re-enroll in 6 months**
- **Medications**
  - Bupropion
  - Varenicline

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