



Safety and Efficacy of Approved and Unapproved Peptide Therapies for Musculoskeletal Injuries and Athletic Performance

Christopher L. Mendias¹ · Tariq M. Awan¹

Accepted: 24 March 2026

© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2026

Abstract

Peptides are short chains of amino acids with a unique pharmacological niche between small-molecule drugs and large proteins. Their use in sports medicine is rapidly expanding, driven by patient demand for accelerated injury recovery and performance enhancement. While numerous peptide drugs have undergone a rigorous approval process that evaluates both safety and efficacy, a parallel “gray market” of unapproved compounds has emerged, operating largely outside of regulatory oversight. Our objective is to present the pharmacological mechanisms, safety profiles, and regulatory status of prominent approved and unapproved peptides marketed direct to patients, including AOD-9604 (anti-obesity drug 9604), BPC-157 (body protection compound 157), CJC-1295, FS-344 (follistatin-344), GHK-Cu (glycyl-L-histidyl-L-lysine copper), ipamorelin, MOTS-C (mitochondrial ORF of the 12S rRNA type-c), sermorelin, SS-31 (elamipretide), tesamorelin (Egrifta), Tβ4 (thymosin beta-4), and TB-500 (thymosin beta-4 fragment). Many unapproved peptides demonstrate favorable tissue repair and metabolic outcomes in animal models, but rigorous human safety data are scarce, and there is potential for serious harm to patients. This narrative review focuses on the utilization of peptides in sports medicine, and alternative treatments that may be considered. We provide a framework to navigate patient discussions about peptides to better facilitate evidence-based practices for musculoskeletal healing and athletic performance. We also discuss the placebo effect as a mediator of peptide efficacy, and how social media amplifies this effect.

1 Introduction

Peptides are molecules composed of up to 40–50 amino acids. Peptides occupy a distinct biochemical and regulatory niche between small-molecule drugs (generally < 500 Daltons) and large biological proteins (> 5000 Daltons), functioning as potent signaling molecules for numerous physiological processes [1, 2]. Peptides have a central role in treating numerous diseases and injuries, including the glucagon-like peptide-1 receptor agonists (GLP-1RAs) tirzepatide and semaglutide, which have revolutionized weight loss and diabetes care [2]. Parathyroid hormone (PTH) analogs abaloparatide and teriparatide are peptides that are critical in treating osteoporosis and accelerating fracture repair [3]. Approved peptide drugs

undergo a rigorous path of development and approval, with extensive clinical trials often consisting of thousands of subjects to establish efficacy and safety [1, 2]. Peptide use is growing, as global sales of approved peptide drugs will likely reach \$75 billion US dollars by 2028 [1]. However, a parallel and pervasive “gray market” has emerged, driven by direct-to-consumer sales of unapproved peptides [4]. These compounds, frequently carrying disclaimers like “research chemical” or “not for human consumption” to circumvent regulatory oversight, are aggressively to the general public through social media and online forums [4]. The purported benefits of these substances include accelerated musculoskeletal injury recovery, muscle hypertrophy, athletic performance enhancement, and many others [4]. As peptides produced on the gray market are not subject to Current Good Manufacturing Practice (cGMP) guidelines or regulatory oversight, there can be considerable risks to patients who use these compounds.

Non-approved peptides present a distinct challenge for sports medicine clinicians. On one hand, animal model data for many peptides show compelling improvements

✉ Christopher L. Mendias
cmendias@performancemedinst.com

¹ Performance Medicine Institute, 3330 N 2nd St Ste 401, Phoenix, AZ 85012, USA

Key Points

Approved peptide therapies offer important benefits to patients, but for many unapproved peptides, there is a profound lack of human clinical data to confirm their safety or efficacy for musculoskeletal injuries and athletic performance.

Peptides purchased through “gray market” channels pose significant health risks because they are produced without regulatory oversight, often containing dangerous impurities, inaccurate dosages, or hidden contaminants.

The perceived benefits of unapproved peptides are often driven by social media influencers and a strong placebo effect, requiring healthcare providers to guide patients toward safer evidence-based alternatives.

in musculoskeletal tissue repair [5–7]. On the other hand, translating these findings to human clinical practice remains largely theoretical, with a profound paucity of human safety data [8]. To align this review with contemporary patient demand, we selected the peptides discussed in this paper based on an analysis of global search popularity, reflecting the significant influence of social media and the gray market. We then evaluated these compounds through a narrative review of the literature, focusing on their pharmacological mechanisms, regulatory status, and the disparity between preclinical findings and human clinical data. Because social media algorithms often create a self-reinforcing cycle of high expectancy and influencer endorsement [9], we discuss the placebo and contextual effects to explain the physiological and psychological drivers of perceived efficacy in the absence of robust clinical evidence. This narrative review will (i) discuss production methods for peptides, (ii) provide an analysis of the most commonly used peptides with sports medicine indications, (iii) describe the placebo and contextual effects of peptides, and (iv) equip providers with the requisite knowledge to facilitate evidence-based discussions with patients.

2 Peptide Synthesis, Manufacturing, and Compounding

To appreciate the risks of gray market peptides, it is important to understand the basics of peptide synthesis. Such understanding is critical to explaining why a “99% pure” label on a gray market vial may still conceal dangerous impurities.

2.1 Peptide Synthesis and Manufacturing

Peptides are generally synthesized through one of three methodologies: solid-phase peptide synthesis, liquid-phase peptide synthesis, or a hybrid approach [2, 10]. Each technique has its strengths and limitations. The disparity between approved pharmaceutical peptides and gray market “research chemicals” is most pronounced in purification and validation steps. Approved peptides undergo stringent purification and validation, while gray market peptides may be produced without these steps [2, 10, 11]. Substitutions or deletions in amino acid residues can result in a peptide with vastly different biological properties, behaving in an unpredictable or dangerous manner [12]. Approved peptides are manufactured in cGMP facilities overseen by regulatory agencies that enforce standardized controls over raw materials, environmental conditions, validated purification processes, and batch testing [2, 11]. In contrast, peptides distributed through gray market channels are produced outside regulated quality systems, and published analyses have demonstrated substantial variability in purity, composition, and the presence of chemical and elemental impurities in these products [11, 13, 14]. Therefore, the lack of regulatory oversight of gray market peptides carries potentially a substantial risk of patient harm.

2.2 Compounding of Approved Peptides

While some approved peptides are produced in large batches by manufacturers under cGMP conditions, smaller batches of approved peptides can be produced via compounding. Peptide compounding in the USA is regulated under Sects. 503A and 503B of the Federal Food, Drug, and Cosmetic Act [15]. Traditional 503A compounding pharmacies compound peptides for individual patients based on a valid prescription and are exempt from cGMP regulations, but must comply with United States Pharmacopeia (USP) standards [16]. Bulk drug substances that have a USP monograph, are components of FDA-approved drugs, or are on approved FDA lists can be legally compounded. Outsourcing facilities (503B) can compound on larger scales without patient-specific prescriptions but must adhere to cGMP standards [16]. The FDA has restricted the compounding of certain peptides, placing them on a “Category 2” list, which effectively bans their compounding. This list includes peptides such as BPC-157, CJC-1295, Ipamorelin, and TB-500, among others [17]. In Europe, pharmaceutical compounding is largely regulated nationally, allowing pharmacists to compound medicines for patients with special needs when a commercial alternative is not available [18]. Australia regulates compounding under the auspices of the Therapeutic Goods Administration (TGA) [19], which generally allows the compounding of peptides entered on the Australian Register of Therapeutic Goods [19].

3 Peptides with Potential Use in Sports Medicine

Peptides with potential impact on muscle size, strength, or athletic performance are rising in popularity. There has been a noticeable increase in direct-to-consumer marketing for unapproved peptides [4]. Consumers are seeking more information on peptides, as evidenced by changes in relative search term popularity. An analysis of Google search trends was conducted to identify peptides most commonly searched for from 2024 onward (Fig. 1). Searches on Google for unapproved peptides such as “AOD-9604,” “BPC-157,” “CJC-1295,” “Follistatin,” “GHK-Cu,” “Ipamorelin,” “MOTS-C,” or “TB-500” have considerably increased starting in 2024 (Fig. 1). This was preceded by searches for approved peptides such as “Tirzepatide” and “Semaglutide” (Fig. 1). Other search terms relevant to sports medicine, such as “Concussion,” “Health,” “Knee injury,” “Weight Loss,” and “Wellness” have remained consistent, while there has been an uptick in “Athletic Performance” (Fig. 1). Many popular peptides relevant to sports medicine are discussed in the following sections and are also summarized in Table 1. We will not discuss the GLP-1RAs or PTH analogs, as these have been covered extensively elsewhere [2, 3]. Peptides discussed below were selected based on Google search trends. Nearly all happen to be on the 2025 World Anti-Doping Agency Prohibited List, with the exception of GHK-Cu and SS-31. We will limit our discussion of alternative treatment options to pharmacological interventions, although for musculoskeletal conditions, treatments such as physiotherapy, platelet-rich plasma, platelet-poor plasma, extracorporeal shockwave therapy, bone marrow aspirate concentrate, or adipose stromovascular fraction therapies [20–23], offer

evidence-based alternatives to peptides with purported musculoskeletal uses. We consider off-label uses of approved medications that have an otherwise established safety profile, and where clinical trial data support their potential use.

3.1 AOD-9604

Anti-obesity drug 9604 (AOD-9604) is a peptide fragment of residues 177–191 of human growth hormone (hGH), with a tyrosine residue added to enhance stability [24]. AOD-9604 was originally developed to isolate the lipolytic properties of hGH while avoiding anabolic and insulin-desensitizing effects [24, 25]. AOD-9604 is proposed to stimulate lipolysis through interaction with beta-adrenergic receptors [24–26]. AOD-9604 does not bind the hGH receptor with high affinity and does not stimulate insulin-like growth factor 1 (IGF-1) production, and aims to reduce adiposity without the other effects of long-term hGH administration [24–26]. AOD-9604 significantly reduced fat mass in rodent models of obesity [26], which then led to six randomized double-blind placebo-controlled trials involving over 900 patients to evaluate the treatment of obesity [25]. The safety profile was favorable, with no changes in IGF-1 or insulin sensitivity [25]. However, AOD-9604 failed to show a dose-dependent, statistically significant effect on weight loss compared to placebo, leading to the termination of clinical development of this peptide for obesity [27].

Recently, there has been interest in AOD-9604 for cartilage repair based on promising results in a rabbit model of osteoarthritis [28], but there are no human data available. While clinical trials demonstrated AOD-9604 was safe in the short term, prolonged activation of beta-adrenergic signaling could lead to dysautonomias [29]. Alternatives to AOD-9604 for weight loss include the GLP-1RAs, or the

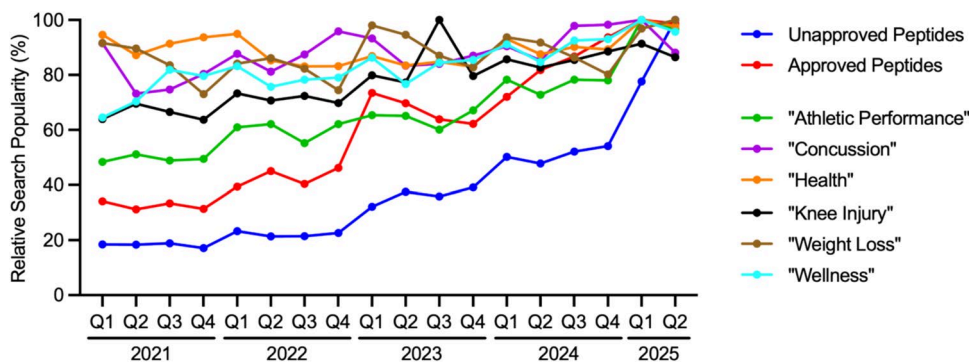


Fig. 1 Google search trend analysis from Quarter 1 (Q1) 2022 through Quarter 2 (Q2) 2025 demonstrating the relative global popularity of search terms or sets of terms. Unapproved peptides consist of the following terms that were analyzed a single relative set: “AOD-9604,” “BPC-157,” “CJC-1295,” “Follistatin,” “GHK-Cu,” “Ipamorelin,” “MOTS-C,” and “TB-500.” Approved peptides consist of the

following terms that were analyzed a single relative set: “Semaglutide,” “Somatropin,” and “Tirzepatide.” For comparison, popularity of other search terms relevant to sports medicine “Athletic Performance,” “Concussion,” “Health,” “Knee injury,” “Weight loss,” and “Wellness” are shown. Q3 Quarter 3, Q4 Quarter 4

Table 1 Summary of peptides discussed in this article

Peptide	Brief description and proposed use	Regulatory status	Clinical trials showing safety and efficacy	Risks ^a	Potential alternatives
AOD-9604 (Anti-Obesity Drug 9604)	C-terminal peptide fragment of hGH; proposed lipolytic and fat loss use	FDA: no EMA: no TGA: no	Safety: yes Efficacy: no	Dysautonomia	GLP-1RA, phentermine
BPC-157 (Body Protection Compound-157)	Peptide found in human gastric secretions; proposed broad regenerative potential and increased angiogenesis	FDA: no EMA: no TGA: no	Safety: no Efficacy: no	Tumor metastasis, worsening of tendon healing	GLP1-RA, tadalafil
CJC-1295	GHRH analog with extended half-life; proposed lipolytic and fat loss use, and muscle hypertrophy	FDA: no EMA: no TGA: no	Safety: no Efficacy: no	Insulin resistance, water retention, organomegaly, death	GLP-1RA, phentermine, testosterone
FS-344 (Follistatin-344)	Peptide that binds to and blocks myostatin and activin signaling, potentially causing muscle hypertrophy	FDA: no EMA: no TGA: no	Safety: yes Efficacy: no	Appears to be safe, but most studies have focused on gene therapy produced FS-344, not infused peptide	Testosterone
GHK-Cu (glycyl-L-histidyl-L-lysine copper complex)	Copper binding peptide; approved for topical cosmetic use; purported wellness and joint healing benefits	FDA: yes (topical) EMA: yes (topical) TGA: yes (topical)	Safety: yes (topical) Efficacy: no	Appears to be safe as an additive for topical cosmetic purposes; injectable formulations could cause copper toxicity and inflammation	GLP-1RA
Ipamorelin	GHSR1 agonist, stimulates hGH and ghrelin release; purported to increase lean mass and improve appetite	FDA: no EMA: no TGA: no	Safety: yes (very limited, 7 days) Efficacy: no	Altered glucose metabolism, decreased insulin sensitivity, somatotroph hyperplasia, adenomas	Dronabinol
MOTS-c (mitochondrial ORF of the 12S rRNA type-c)	Mitochondrial-derived peptide purported to be an exercise mimetic, decrease fat mass, and improve insulin sensitivity	FDA: no EMA: no TGA: no	Safety: no Efficacy: no	Altered folate metabolism and nucleotide biosynthesis	GLP-1RA, metformin, phentermine, SGLT2 inhibitors, thiazolidinediones
Sermorelin	N-terminal fragment of GHRH, hGH secretagogue; purported body fat reduction and aid in connective tissue healing	FDA: yes EMA: no TGA: yes	Safety: yes Efficacy: yes	Facial flushing, headache, dizziness, hypoglycemia	GLP-1RA, phentermine
SS-31 (elamipretide)	Tetrapeptide that stabilizes inner mitochondrial membrane, improves metabolic efficiency, reduced mitochondrial myopathy symptoms, and reduces reactive oxygen species	FDA: yes EMA: pending TGA: no	Safety: yes Efficacy: yes	Headache, fatigue, malaise	None
Tβ4 (thymosin beta-4)	43-Amino acid peptide that sequesters G-actin, wound healing, and injury repair	FDA: no EMA: no TGA: no	Safety: yes Efficacy: minimal	Headache, fatigue, malaise, cancer metastasis	None

Table 1 (continued)

Peptide	Brief description and proposed use	Regulatory status	Clinical trials showing safety and efficacy	Risks ^a	Potential alternatives
TB-500 (thymosin beta-4 fragment)	Synthetic fragment of active site of thymosin beta-4, purported to improve wound healing and recovery after exercise	FDA: no EMA: no TGA: no	Safety: no Efficacy: no	Headache, fatigue, malaise, cancer metastasis	None
Tesamorelin	Full amino acid sequence of GHRH modified with trans-3-hexenoic acid group; visceral fat reduction and purported benefits for connective tissue healing	FDA: yes EMA: no TGA: no	Safety: yes Efficacy: yes	Facial flushing, headache, dizziness, hypoglycemia	GLP-1RA, phentermine

GHRH growth hormone-releasing hormone, *GHSRI* ghrelin/growth hormone secretagogue receptor 1, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *hGH* human growth hormone, *SGLT2* sodium-glucose transport protein 2

See article for detailed discussion

^aAll peptides produced outside of Current Good Manufacturing Practice guidelines may carry risks of endotoxin, heavy metals, microbial contamination and non-sterility, inaccurate peptide identity or concentration, residual solvents and reagents from synthesis, unexpected degradation products and aggregates, mislabeled or substituted active ingredients, and untested impurities such as counterions, particulates, and other toxic byproducts that would normally be identified and controlled in a regulated manufacturing environment

norepinephrine and dopamine-releasing agent phentermine [30–32], which are approved for weight loss. Emerging data indicate that GLP-1RAs also appear to be effective in reducing joint pain and inflammation, with a potential role in treating arthritis [33].

3.2 BPC-157

Body protection compound-157 (BPC-157) is a 15-amino acid peptide derived from a protein found in human gastric secretions [5]. BPC-157 is thought to act through multiple biochemical pathways to promote tissue repair, but activating vascular endothelial growth factor (VEGF) signaling appears to be its main mode of action [5, 34]. Preclinical data demonstrate BPC-157 can potentially be effective in healing musculoskeletal injuries [34], but clinical validation in human subjects is virtually non-existent. A small retrospective observational report described self-reported improvements in knee pain following intra articular BPC-157 injections [35]. However, the study was fraught with several critical flaws, including the absence of a control group, reliance on subjective patient recall, and the lack of validated outcome measures, among others. The study is therefore at high risk of bias, substantially limiting the strength and generalizability of its findings.

Social media influencers have promoted BPC-157 for the treatment of chronic musculoskeletal injuries and pain, often citing the proposed effects of BPC-157 on blood flow. A major concern about the safety of BPC-157 stems from its role in stimulating angiogenesis via VEGF signaling. High VEGF abundance in tumor tissue or blood is consistently associated with worse outcomes in cancer treatment [36]. Additionally, while vascularization may improve healing in some tissues, neovascularization is correlated with worse functional outcomes in chronic tendinopathy [37, 38]. A safer evidence-based alternative to BPC-157 for improving vascular function could be the phosphodiesterase-5 inhibitor tadalafil, which improves vascular function through increasing circulating endothelial progenitor cells and enhancing flow-mediated dilation [39]. Tadalafil also appears to improve pain and quality of life in patients with chronic pelvic pain syndrome [40]. An additional potential alternative to BPC-157 for the treatment of arthralgias are the GLP-1RAs, which appear to reduce joint pain and inflammation through a combination of direct weight loss as well as intraarticular anti-inflammatory and chondroprotective effects [33].

3.3 CJC-1295

CJC-1295 is a synthetic analog of growth hormone-releasing hormone (GHRH) and has a significantly extended half-life compared with endogenous GHRH [41]. CJC-1295 is a

GHRH agonist, binding to GHRH receptors in the pituitary gland to stimulate hGH secretion and IGF-1 production. CJC-1259 causes a sustained, rather than pulsatile, elevation of hGH in human subjects, with a 2- to tenfold increase in hGH for 6 days or more post-injection [41]. There are significant safety concerns with CJC-1295. In a dose-escalation trial, adverse events occurred in 94% of patients receiving CJC-1295, while only 29% of subjects receiving a placebo reported similar events [41]. These side effects included injection-site reaction, headache, diarrhea, and systemic vasodilatory responses [41]. A phase II trial of CJC-1295 to treat HIV-associated lipodystrophy was halted after the death of a patient, although the causality regarding CJC-1295 was debated [42].

Social media influencers have promoted the use of CJC-1295 to increase muscle mass, reduce fat, and improve tissue healing. CJC-1295 is sometimes suggested by social media influencers to be combined with ipamorelin to try to maximize hGH pulse amplitude while attempting to mitigate continuous GHRH stimulation issues. However, continuous elevation of hGH can cause pituitary desensitization and blunting of the natural hGH axis [43]. Persistent activation of the hGH-IGF-1 axis can cause insulin resistance, water retention, and organomegaly [44]. Safer and likely more effective treatment options to CJC-1295 for body fat reduction include GLP-1RAs or phentermine, which are approved for this indication [30–32]. For increasing muscle mass, a limited course of low-dose testosterone has been proposed as a potential alternative in patients with focal muscle atrophy [45].

3.4 FS-344

Follistatin is a naturally occurring autocrine glycoprotein. The 344 isoform (FS-344) is an alternatively spliced peptide that inhibits myostatin and activin signaling [46]. Myostatin and activin induce muscle atrophy, and by sequestering inhibitors of atrophy, FS-344 is posited to increase muscle mass and strength [46, 47]. FS-344 has gained traction in the gray market because of its potential ability to induce muscle hypertrophy.

Adeno-associated viral gene-mediated delivery of FS-344 has shown dramatic increases in muscle mass and strength in mouse and non-human primate models [7, 48]. A small clinical trial in patients with Becker muscular dystrophy showed safety and functional improvements with FS-344 adeno-associated viral gene therapy [49]. An important distinguishing factor between gene therapy and injectable FS-344 is the relatively short 1- to 2-h half-life of follistatin [50]. The gene vector that produces FS-344 utilizes the cytomegalovirus promoter, which is a constitutively active promoter [51], resulting in near-constant production of FS-344 in transduced cells. As a therapeutic peptide, FS-344

would therefore likely need to be infused constantly or dosed numerous times per day to effectively suppress myostatin and activin signaling. The need for frequent administration means that FS-344 is likely to have little practical utility as a peptide therapy. Safety studies of injectable FS-344 are limited, with most focused on the gene therapy. Alternative approaches to using FS-344 potentially include low-dose testosterone, which has been proposed to increase muscle mass in patients with muscle atrophy that occurs secondary to a bone or joint injury [45].

3.5 GHK-Cu

GHK-Cu (glycyl-L-histidyl-L-lysine copper complex) is a naturally occurring, copper-binding peptide. Originally isolated from human plasma [52], topical GHK-Cu promotes collagen synthesis, stimulates angiogenesis, and possesses antioxidant and anti-inflammatory properties through cytokine downregulation [52]. In humans, GHK-Cu is widely used in cosmetics to improve skin texture and composition [52]. In the USA, Europe, and Australia, GHK-Cu is not approved as a drug for topical use but is allowed as a cosmetic product owing to minimal systemic absorption.

Much of the promotion of GHK-Cu on social media has focused not just on topical use, but also oral consumption for overall wellness, or injectable formulations to treat joint pain. While topical GHK-Cu has a long history of safe cosmetic use [52], injectable forms pose distinct risks. When taken orally, similar to other proteins, the peptide component of GHK-Cu would likely undergo rapid proteolytic degradation in the gastrointestinal tract, releasing free copper ions. This would effectively convert GHK-Cu into an oral copper supplement rather than delivering the intact peptide complex systemically. Ingesting high levels of soluble copper salts can cause gastrointestinal and liver toxicity [53]. Within the joint, excess copper promotes aggregation of lipoylated tri-carboxylic acid cycle enzymes and destabilization of iron-sulfur clusters, thereby impairing mitochondrial integrity leading to chondrocyte death [54]. No direct approved alternative medications are available for promoting joint healing, although GLP-1RAs appear to be effective in treating joint pain [33].

3.6 Ipamorelin

Ipamorelin is a pentapeptide and a selective agonist of the ghrelin/growth hormone secretagogue receptor 1 that stimulates the pituitary gland to release hGH in a pulsatile manner [55]. Unlike other ghrelin/growth hormone secretagogue receptor 1 agonists, ipamorelin does not significantly stimulate the release of cortisol or prolactin [56]. Animal studies demonstrate ipamorelin may function similar to other hGH secretagogues as it relates to musculoskeletal effects

[57]. However, unlike other hGH secretagogues, ipamorelin appears to stimulate food intake and adiposity through activation of the ghrelin receptor [58]. Activation of the ghrelin receptor also appears to reduce colonic hypersensitivity, and visceral and somatic allodynia [59]. A small phase II study of ipamorelin was conducted in patients with postoperative ileus, and found that a 7-day treatment course of the peptide was generally safe, but had no impact on clinical outcomes [60]. Ipamorelin also has been marketed on social media as an orexigenic agent to aid individuals consuming high-protein diets overcome the satiety-inducing effects of protein, although there are no human studies that directly support this indication.

Large clinical trials and compelling safety data for the use of ipamorelin are lacking, and there are some potentially serious concerns with the use of this peptide. Chronic stimulation of the ghrelin receptor can alter glucose metabolism and insulin sensitivity [61]. Because the ghrelin receptor is highly expressed in somatotroph adenomas and ghrelin can stimulate proliferation of somatotroph tumor cells, there is a concern that chronic non-physiologic ghrelin/growth hormone secretagogue receptor activation could contribute to somatotroph hyperplasia or adenoma formation [62]. Alternatives to ipamorelin may be the use of more calorie-dense foods that have a higher number of calories per volume, or cannabinoid receptor agonists such as dronabinol that can increase appetite [63, 64].

3.7 MOTS-C

MOTS-c (mitochondrial ORF of the 12S rRNA type-c) is a peptide encoded by the mitochondrial genome that is thought to act as an exercise mimetic, interacting with the folate cycle and AMPK pathways to regulate glucose metabolism and insulin sensitivity [6, 65]. MOTS-c works in preclinical models by promoting fatty acid oxidation and inhibiting folate-dependent purine biosynthesis. MOTS-c prevented diet-induced obesity and insulin resistance in mice [6, 65]. Human data are limited to observational studies correlating endogenous MOTS-c levels with insulin sensitivity [6, 65], and clinical trials exploring the therapeutic use of MOTS-c have not been completed.

MOTS-c has been marketed online for endurance enhancement, weight loss, and metabolic improvements. There is a theoretical risk that long-term dosing of MOTS-c could disrupt cellular replication or nucleotide biosynthesis in unforeseen ways. The metabolic consequences of chronic AMPK activation in healthy humans are also not fully understood [66]. Safe and effective alternatives to MOTS-c for weight loss include the GLP-1RAs or phentermine [30, 31]. For improving insulin sensitivity, there are a variety of alternatives, including metformin, thiazolidinediones, sodium-glucose transport protein 2 inhibitors, and GLP-1RAs [67].

3.8 Sermorelin and Tesamorelin

Sermorelin and tesamorelin are hGH secretagogue peptides with similar biological properties. Sermorelin is a synthetic N-terminal fragment (1–29) of GHRH and was previously FDA approved for pediatric growth failure under the brand name Geref, but was discontinued by the manufacturer in 2008 for commercial reasons [68]. As sermorelin was not withdrawn for safety reasons, the FDA and TGA generally allow sermorelin to be prescribed by a physician and legally compounded. Tesamorelin (Egrifta) is an FDA-approved peptide consisting of the full 44-amino acid sequence of GHRH modified with the trans-3-hexenoic acid group, which increases the half-life and potency of hGH axis stimulation [69, 70]. While not approved by the European Medicines Agency or TGA, tesamorelin is FDA approved for visceral fat reduction in HIV + patients with lipodystrophy.

Sermorelin and tesamorelin stimulate the physiological pulsatile release of hGH and increase serum IGF-1 [70]. These peptides are potentially safer than exogenous hGH because they preserve feedback control of both GH and IGF-1 and protect against imbalances between growth hormone and IGF-1 levels [70]. Much of the research on sermorelin and tesamorelin has focused on changes in body composition. In human subjects treated with sermorelin for 6 weeks, there was an increase in nocturnal hGH release and peak amplitude, with no changes in body weight, body mass index, waist-to-hip ratio, or body composition [71]. A 5-month treatment course of [Nle27]GHRH-(1–29)-NH₂, which is a molecule identical to sermorelin with the exception of a single amino acid substitution of methionine for norleucine at residue 27, increased lean body mass by 2.3% in men, with no change in fat mass [72]. In HIV + individuals with lipodystrophy who were treated with tesamorelin for 6 months, there was a 15% reduction in visceral fat, a 7.3% reduction in overall trunk fat, a 2.5% reduction in waist circumference, and a 2.2% increase in lean mass [73]. For obese subjects with reduced hGH secretion treated with a 12-month course of tesamorelin, there was a 7.7% decrease in visceral fat, a 2.6% reduction in trunk fat, a 1.7% decrease in waist circumference, and a 1.4% increase in lean mass [74].

Outside of body composition, sermorelin and tesamorelin have been promoted on social media for recovery from musculoskeletal injuries and improved athletic performance. Although there is not direct clinical data to support these peptides directly in tissue healing, there is limited but encouraging preclinical and clinical data demonstrating hGH can improve outcomes for musculoskeletal injuries. The purported effects of sermorelin and tesamorelin on tissue healing and athletic performance are often extrapolated based on their ability to raise hGH and IGF1, even if the studies did not directly analyze these peptides. As it relates to tissue

healing, hGH appears to increase connective tissue collagen synthesis, protect against muscle weakness after joint injury, and reduce biomarkers of osteoarthritis after joint injury [75–77]. Human growth hormone has been proposed to have anti-aging effects, although this is controversial [78]. While short-term use of hGH appears to offer therapeutic benefits for some conditions [70], organisms with sustained elevations in hGH over several years typically have shorter lifespans [78]. Alternatives to the use of sermorelin or tesamorelin for visceral fat reduction include the GLP-1RAs and phentermine [31, 79].

3.9 SS-31

SS-31 (elamipretide) is a tetrapeptide that binds selectively to cardiolipin, a phospholipid in the inner mitochondrial membrane, resulting in improved electron transport chain efficiency [80]. SS-31 underwent rigorous development and was recently approved by the FDA for Barth syndrome [81], with European Medicines Agency and TGA approval pending. SS-31 reduces the production of intracellular reactive oxygen species, and has shown efficacy in heart failure, ischemia–reperfusion injury, and mitochondrial myopathies [80]. SS-31 is generally well tolerated with no major side effects [80]. Additionally, preclinical studies demonstrate that SS-31 improves cognitive function in traumatic brain injuries [82], suggesting a potential role in treating patients with concussions.

Social media has promoted gray market SS-31 to improve endurance and recovery. While SS-31 has recently achieved regulatory approval for a severe metabolic myopathy [81], the safety and efficacy profile in healthy individuals for performance enhancement or injury recovery remains largely unstudied. Preclinical studies in mice demonstrated SS-31 increased treadmill endurance and reduced fatigue [83]. In humans, a single 2-h infusion of elamipretide acutely improved mitochondrial ATP production capacity in skeletal muscle, but this did not translate to reduced muscle fatigability [84]. SS-31 is relatively unique in its class, and no currently approved drugs function in a similar manner.

3.10 T β 4 and TB-500

Thymosin beta-4 (T β 4) is a 43-amino acid peptide that functions as a G-actin sequestering molecule [85]. TB-500 is a synthetic 7-amino acid peptide corresponding to amino acids 17–23 of T β 4, which represents the central actin-binding domain that has cell migration and wound healing functions [86]. T β 4 has been relatively well studied in preclinical models, and some limited clinical studies, while research on TB-500 has been focused more on characterization of the peptide than evaluation of its safety and efficacy. After injury, T β 4 is released by platelets, macrophages, and other

immune cells to help initiate the tissue repair cascade [87]. In preclinical models, T β 4 has demonstrated broad regenerative effects across multiple tissue types. T β 4 accelerated healing of full-thickness dermal wounds in normal, diabetic, steroid-treated, and aged mice, with reduced scarring and improved collagen organization [88]. In skeletal muscle injury models, T β 4 acted as a chemoattractant for muscle stem cells and increased regenerating muscle fibers, though this did not translate to improvements in strength [89]. Phase I clinical trials focused on safety have generally found short-term use of T β 4 to be safe, with similar adverse-event profiles between placebo- and drug-treated groups [90, 91]. An ophthalmic formulation of T β 4 has been studied in small clinical trials of a rare corneal disease, neurotrophic keratopathy, and T β 4 applied to the surface of the cornea appears to be safe and effective [92]. A clinical trial evaluating T β 4 in myocardial infarctions was shown to be safe, with mixed results on efficacy for infarct size [93].

The purported use of T β 4 and TB-500 on social media often centers around injury recovery and metabolic substrate restoration after endurance exercise, but human data are lacking. While there are some encouraging preclinical data, there are no indications of the clinical efficacy of T β 4 or TB-500 for safely improving musculoskeletal repair or athletic performance. There are also significant safety concerns about the use of these peptides. T β 4 is overexpressed in multiple tumor types, including colorectal, pancreatic, breast, and lung cancers, and elevated T β 4 levels correlate with tumor progression, metastasis, and poor prognosis [94]. T β 4 promotes epithelial-mesenchymal transition, a process often involved in cancer metastasis, and enhances tumor angiogenesis through the same mechanisms that promote wound healing [95]. While a causal role for exogenous T β 4 in tumorigenesis has not been established, the theoretical risk of promoting occult malignancies or accelerating tumor growth warrants caution, particularly with long-term use. Although T β 4 has been reasonably well studied, very little is known about TB-500. These peptides are relatively unique and there are no approved drugs with similar mechanisms of action.

4 Placebo and Contextual Effects of Peptides

Placebos are interventions that lack specific pharmacologic activity for the condition being treated, but can have a considerable impact on physiological function [96]. Related to this, the contextual effect of therapy is a complex psychological event that encompasses the placebo medication, as well as the ritual encompassing patient expectations, injections and procedures, interactions from other patients and peers, and the opinions and endorsements from trusted

figures and medical professionals [96]. Contextual effects can result in robust physiological changes, even though the compound that is being consumed has no direct pharmacologic mechanism of action [96]. When the compound does have a pharmacological mechanism of action, contextual effects can modulate the efficacy of the therapeutic intervention [96].

Peptides constitute near-ideal factors for amplified contextual effects because they often combine high expectancy, invasive injections, and endorsement from popular social media influencers with a dense therapeutic ritual. As it relates to pain, contextual effects can engage endogenous opioid signaling within numerous brain structures and can be attenuated or abolished by naloxone, indicating a genuine modulation of descending pain control systems rather than reporting bias alone [97]. Contextual effects can also

induce dopaminergic signaling within mesolimbic reward circuits to further connect the expectation of a positive effect of a placebo to pain reduction [97]. Dopaminergic activation can contribute to polypharmacy [98], and in the case of peptides, the use of one peptide to treat a specific condition could motivate a patient to seek additional peptides to treat other conditions. Outside of the brain, contextual effects can also impact local immune cell function and tissue repair, resulting in alterations in cytokine profiles and immune cell activation [99].

Contextual effects appear to have small-to-moderate effects on musculoskeletal pain and athletic performance [100–103]. Even in open-label studies where subjects knew they were receiving a pharmacologically inert pill, placebo treatment still improved pain and function, demonstrating the considerable power of contextual effects [104]. The manner in

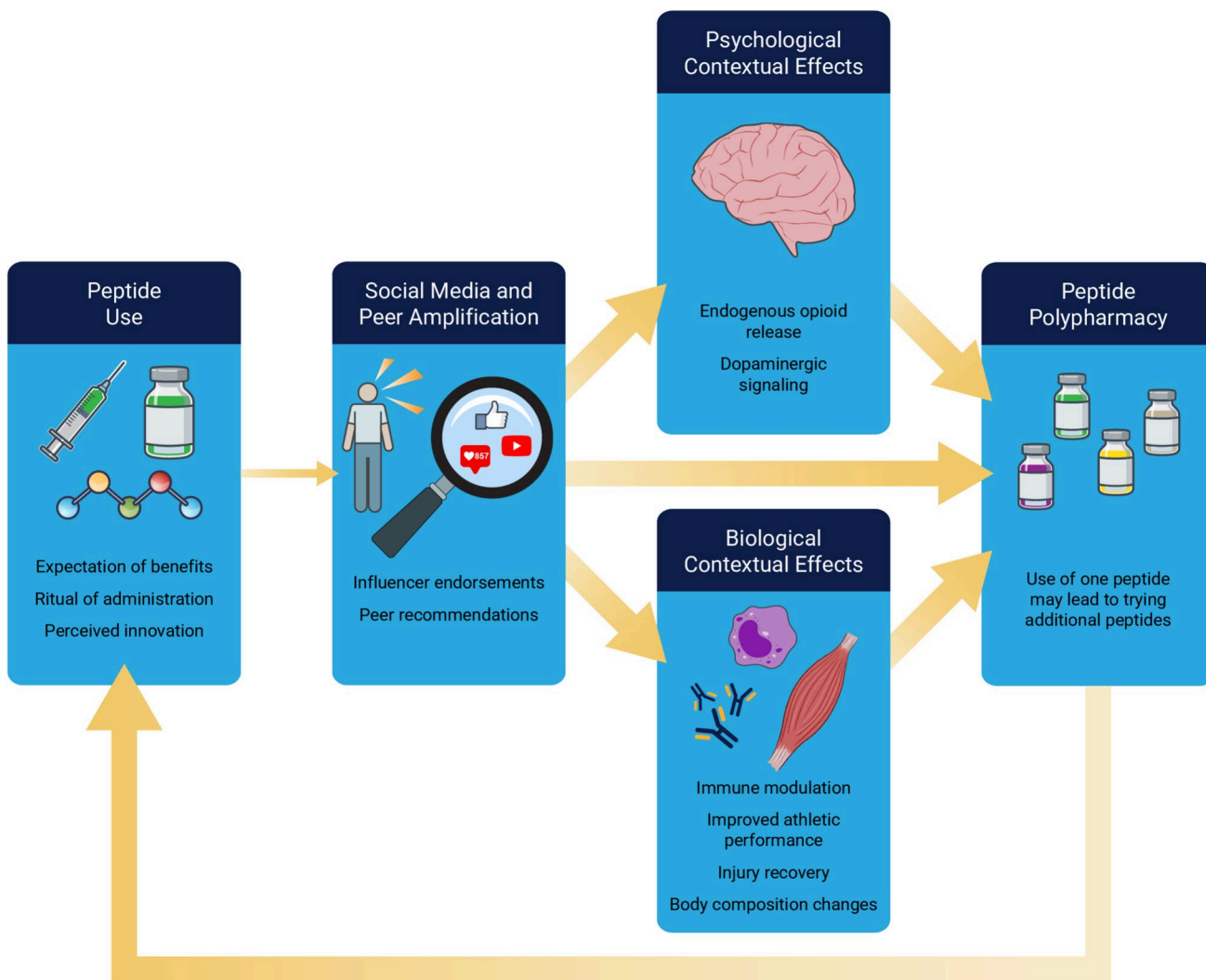


Fig. 2 Proposed model of the reinforcing cycle of social media and peer amplification leading to placebo and contextual effects. Illustration of how peptide use is influenced by factors such as expectations and rituals, and is further amplified by social media and peer endorse-

ments. These trigger psychological and biological context-dependent effects. These positive reinforcing effects motivate the user to try additional peptides, leading to polypharmacy and creating a feedback loop that perpetuates continued use

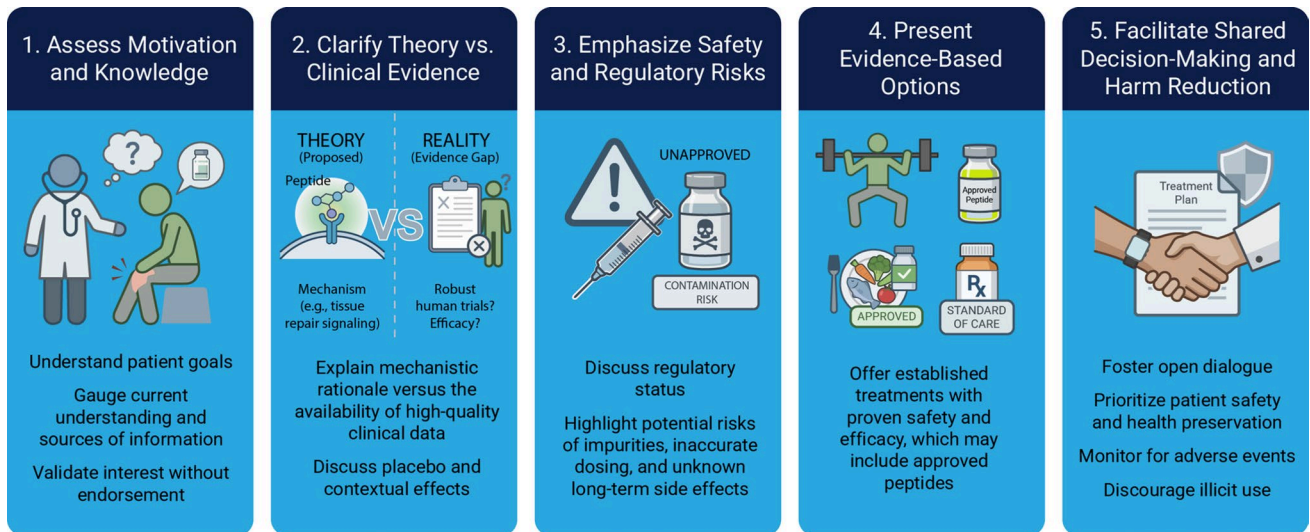


Fig. 3 Discussing peptides with patients. A five-step theoretical framework for clinicians to discuss peptides with patients

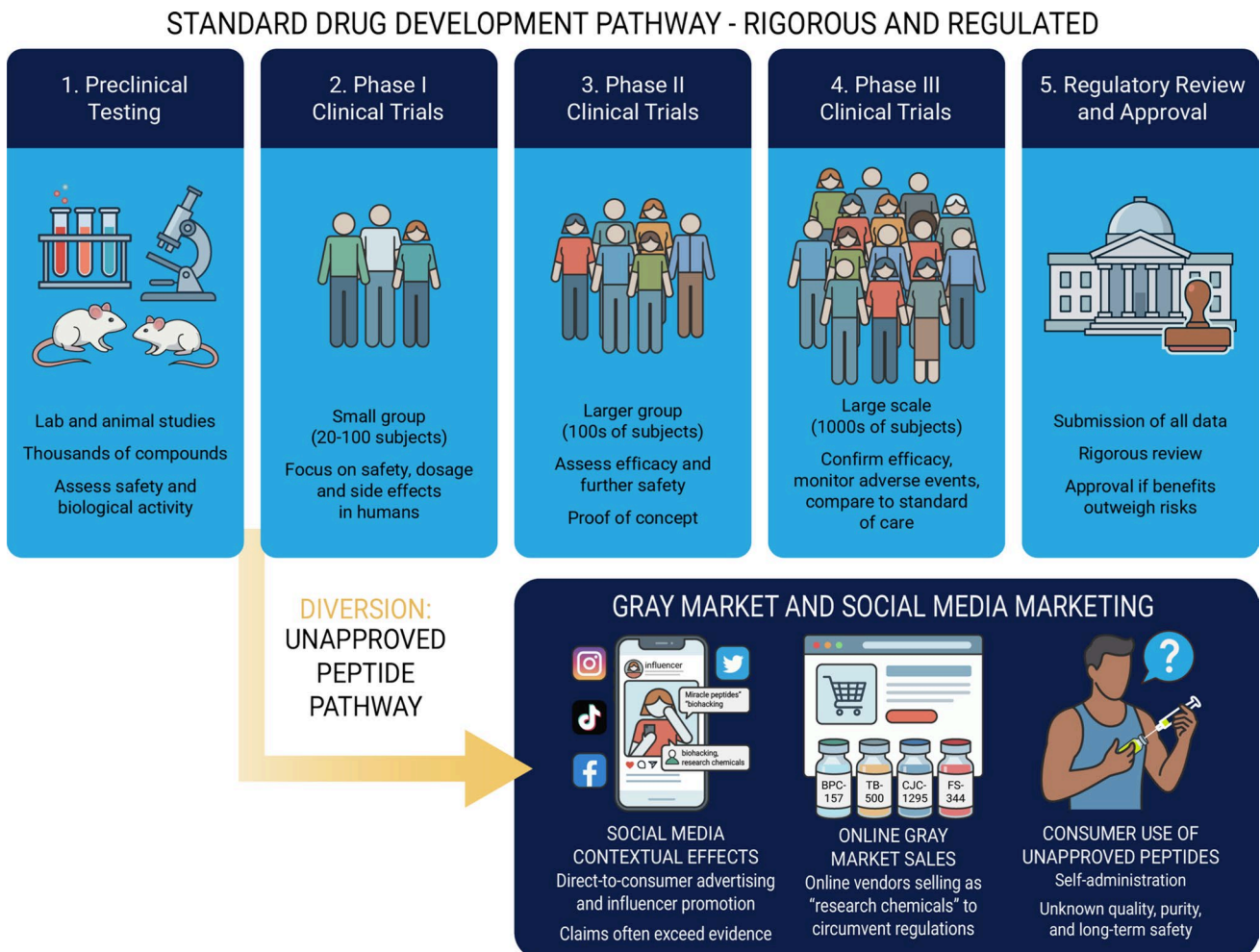
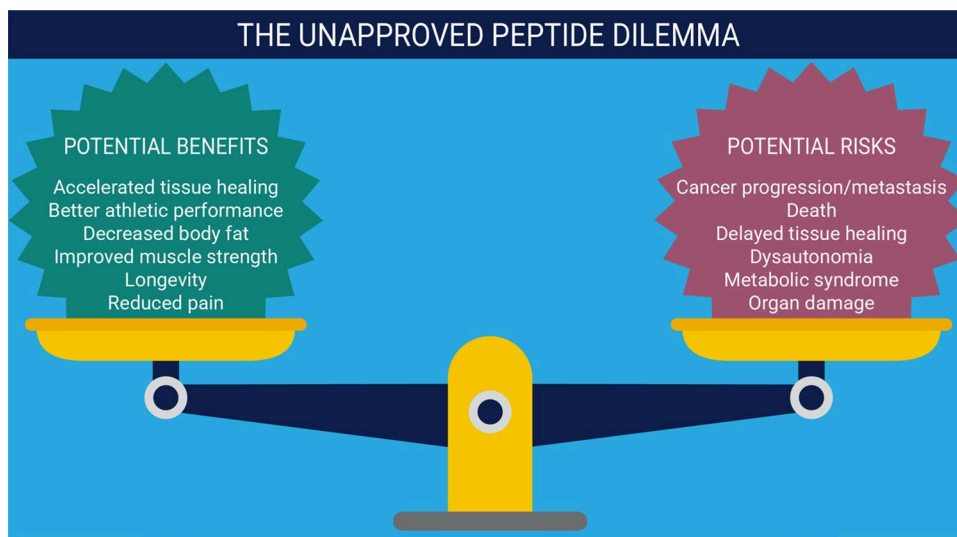


Fig. 4 Standard drug development pathway compared with gray market distribution of unapproved peptides. The regulatory process for drugs approval is shown in the upper panel. The lower pathway illustrates diversion of peptides into an unapproved market

Fig. 5 Overview of the unapproved peptide dilemma. The potential benefits and risks of unapproved peptides



which contemporary social media platforms reinforce interest [105] likely contributes to the contextual effects of peptide therapy. An individual who is interested in athletic performance or injury recovery may receive ads for a company selling peptides, or may have videos of influencers promoting peptides appear in their suggested viewing lists. Once the individual clicks on the ad or suggested video, a positive feedback cycle is engaged [105], which fills their social media feed with content promoting peptides. Health information delivered through social media often has an overemphasis on potential positive effects and preclinical studies without a balanced discussion of the human clinical trials or potential side effects [106, 107]. For peptides with no effective pharmacological mechanism, contextual marketing effects may be enough for an individual to feel benefit with peptide use. Peptides with an established pharmacological mechanism could have even more of a positive effect. The average time a user spends on social media continues to increase [108], so it is likely that contextual effects around peptides will continue to grow, making informed decisions with providers about evidence-based peptides even more important (Fig. 2). Additionally, potential positive effects of the peptide need to be weighed against potential negative effects, such as cancer metastasis or mortality.

5 Discussing Peptide Therapy with Patients

Sports medicine providers increasingly encounter patients who want to incorporate peptides in their treatment program. However, much of the motivation patients have for peptides is based on biased advertising, online forums, or gray market vendor websites [4]. Navigating these conversations requires an approach that effectively contrasts marketing narratives with results from objective peer-reviewed studies.

The general framework we propose to discuss peptide therapies with patients is as follows. First, clinicians should determine patient goals such as recovery or performance improvement, and gauge patient understanding and interest in peptides. Second, clarify theory versus clinical data by explaining the proposed mechanisms for a peptide, the available scientific evidence, and the impact of placebo and contextual effects. Third, safety risks should be emphasized by highlighting the potential for contamination, inaccurate dosing, and unknown long-term side effects. Fourth, present evidence-based alternatives of established treatments with proven safety and efficacy that align with the patient goals. Finally, shared decision making should occur, prioritizing patient safety and health preservation, and monitoring for adverse events if peptide use is suspected, while at the same time discouraging illicit use. An overview is presented in Fig. 3. We review additional discussion points in the Electronic Supplementary Material.

6 Conclusions

The integration of peptide therapy into sports medicine brings considerable opportunities to improve outcomes, yet the landscape is fraught with significant regulatory and safety hazards. While molecules like BPC-157 and T β 4 demonstrate impressive healing properties in animals, the translation to humans is stalled by a lack of rigorous controlled trials. Of 5000 drug candidates that enter preclinical testing, on average only five are tested in human trials, and only one of the five compounds is eventually approved for use [109]. Future progress depends on moving peptides out of the gray market and into the transparent light of pharmaceutical development and clinical trials (Fig. 4). Until high-quality data emerge for unapproved peptides,

sports medicine professionals must educate patients on the scientific rationale, placebo and contextual effects, and the potential risks with using unapproved compounds (Fig. 5). Clinical trials and robust safety data are needed now more than ever to bridge the widening chasm between myths perpetuated online and actual science.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40279-026-02437-0>.

Funding No funding was received to assist with the preparation of this article.

Declarations

Conflicts of interest/competing interests Tariq M. Awan receives consulting fees from Arthrex for activities unrelated to topics discussed in this article. Christopher L. Mendias has no conflicts of interest that are directly relevant to the content of this article.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' contributions CLM and TMA conceived the study; CLM drafted the manuscript; CLM and TMA edited the manuscript, and read and approved the final version of the manuscript and agree with the order of presentation of the authors.

References

- Otvos L, Wade JD. Big peptide drugs in a small molecule world. *Front Chem.* 2023;11:1302169. <https://doi.org/10.3389/fchem.2023.1302169>.
- Wang L, Wang N, Zhang W, Cheng X, Yan Z, Shao G, et al. Therapeutic peptides: current applications and future directions. *Signal Transduct Target Ther.* 2022;7:48. <https://doi.org/10.1038/s41392-022-00904-4>.
- Bonnet A-L, Aboishava L, Mannstadt M. Advances in parathyroid hormone-based medicines. *J Bone Miner Res.* 2025;40:1195–206. <https://doi.org/10.1093/jbmr/zjaf118>.
- Turnock DL, Gibbs DN. Click, click, buy: the market for novel synthetic peptide hormones on mainstream e-commerce platforms in the UK. *Perform Enhanc Health.* 2023;11:100251. <https://doi.org/10.1016/j.peh.2023.100251>.
- Józwiak M, Bauer M, Kamysz W, Kleczkowska P. Multifunctionality and possible medical application of the BPC 157 peptide: literature and patent review. *Pharmaceuticals Basel.* 2025;18:185. <https://doi.org/10.3390/ph18020185>.
- Zheng Y, Wei Z, Wang T. MOTS-c: a promising mitochondrial-derived peptide for therapeutic exploitation. *Front Endocrinol.* 2023;14:1120533. <https://doi.org/10.3389/fendo.2023.1120533>.
- Haidet AM, Rizo L, Handy C, Umapathi P, Eagle A, Shilling C, et al. Long-term enhancement of skeletal muscle mass and strength by single gene administration of myostatin inhibitors. *Proc Natl Acad Sci USA.* 2008;105:4318–22. <https://doi.org/10.1073/pnas.0709144105>.
- McGuire FP, Martinez R, Lenz A, Skinner L, Cushman DM. Regeneration or risk? A narrative review of BPC-157 for musculoskeletal healing. *Curr Rev Musculoskelet Med.* 2025;18:611–9. <https://doi.org/10.1007/s12178-025-09990-7>.
- De D, Jamal ME, Aydemir E, Khera A. Social media algorithms and teen addiction: neurophysiological impact and ethical considerations. *Cureus.* 2025;17:e77145. <https://doi.org/10.7759/cureus.77145>.
- Sharma A, Kumar A, Torre BGdela, Albericio F. Liquid-phase peptide synthesis (LPPS): a third wave for the preparation of peptides. *Chem Rev.* 2022;122:13516–46. <https://doi.org/10.1021/acs.chemrev.2c00132>.
- Janvier S, Cheyns K, Canfyn M, Gosciny S, Spiegeleer BD, Vanhee C, et al. Impurity profiling of the most frequently encountered falsified polypeptide drugs on the Belgian market. *Talanta.* 2018;188:795–807. <https://doi.org/10.1016/j.talanta.2018.06.023>.
- D'Hondt M, Bracke N, Taevernier L, Gevaert B, Verbeke F, Wynendaele E, et al. Related impurities in peptide medicines. *J Pharm Biomed Anal.* 2014;101:2–30. <https://doi.org/10.1016/j.jpba.2014.06.012>.
- Janvier S, Sutter ED, Wynendaele E, Spiegeleer BD, Vanhee C, Deconinck E. Analysis of illegal peptide drugs via HILIC-DAD-MS. *Talanta.* 2017;174:562–71. <https://doi.org/10.1016/j.talanta.2017.06.034>.
- Høj LJ, Rasmussen BS, Dalsgaard PW, Linnet K. Analysis of seized peptide and protein-based doping agents using four complementary methods: liquid chromatography coupled with time of flight mass spectrometry, liquid chromatograph-ultraviolet, Bradford, and immunoassays. *Drug Test Anal.* 2021;13:1457–63. <https://doi.org/10.1002/dta.3026>.
- Sood N, Garg R. Global rise of compounded weight-loss medicines: a worrisome trend. *J Endocr Soc.* 2025;9:bvaf084. <https://doi.org/10.1210/jendso/bvaf084>.
- DiStefano MJ, Dardouri M, Moore GD, Saseen JJ, Nair KV. Compounded glucagon-like peptide-1 receptor agonists for weight loss: the direct-to-consumer market in Colorado. *J Pharm Policy Pract.* 2025;18:2441220. <https://doi.org/10.1080/20523211.2024.2441220>.
- US FDA. Certain bulk drug substances for use in compounding that may present significant safety risks. <https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>. Accessed 1 Mar 2026.
- Carvalho M, Almeida IF. The role of pharmaceutical compounding in promoting medication adherence. *Pharmaceuticals.* 2022;15:1091. <https://doi.org/10.3390/ph15091091>.
- Yoffe A, Liu J, Smith G, Chisholm O. Regulatory reform outcomes and accelerated regulatory pathways for new prescription medicines in Australia. *Ther Innov Regul Sci.* 2023;57:271–86. <https://doi.org/10.1007/s43441-022-00465-2>.
- Chung B, Wiley JP. Extracorporeal shockwave therapy. *Sports Med.* 2002;32:851–65. <https://doi.org/10.2165/00007256-200232130-00004>.
- Andia I, Maffulli N. Biological therapies in regenerative sports medicine. *Sports Med.* 2017;47:807–28. <https://doi.org/10.1007/s40279-016-0620-z>.
- Hudgens JL, Sugg KB, Grekin JA, Gumucio JP, Bedi A, Mendias CL. Platelet-rich plasma activates proinflammatory signaling pathways and induces oxidative stress in tendon fibroblasts. *Am J Sports Med.* 2016;44:1931–40. <https://doi.org/10.1177/0363546516637176>.

23. Malliaras P, Barton CJ, Reeves ND, Langberg H. Achilles and patellar tendinopathy loading programmes. *Sports Med.* 2013;43:267–86. <https://doi.org/10.1007/s40279-013-0019-z>.
24. Cox HD, Smeal SJ, Hughes CM, Cox JE, Eichner D. Detection and in vitro metabolism of AOD9604. *Drug Test Anal.* 2015;7:31–8. <https://doi.org/10.1002/dta.1715>.
25. Stier H, Vos E, Kenley D. Safety and tolerability of the hexadecapeptide AOD9604 in humans. *J Endocrinol Metab.* 2013;3:7–15. <https://doi.org/10.4021/jem157w>.
26. Heffernan M, Summers RJ, Thorburn A, Ogru E, Gianello R, Jiang W-J, et al. The effects of human GH and its lipolytic fragment (AOD9604) on lipid metabolism following chronic treatment in obese mice and β 3-AR knock-out mice. *Endocrinology.* 2001;142:5182–9. <https://doi.org/10.1210/endo.142.12.8522>.
27. Valentino MA, Lin JE, Waldman SA. Central and peripheral molecular targets for antiobesity pharmacotherapy. *Clin Pharmacol Ther.* 2010;87:652–62. <https://doi.org/10.1038/clpt.2010.57>.
28. Kwon DR, Park GY. Effect of intra-articular injection of AOD9604 with or without hyaluronic acid in rabbit osteoarthritis model. *Ann Clin Lab Sci.* 2015;45:426–32.
29. Fedorowski A. Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management. *J Intern Med.* 2019;285:352–66. <https://doi.org/10.1111/joim.12852>.
30. Bhandarkar A, Bhat S, Kapoor N. Effect of GLP-1 receptor agonists on body composition. *Curr Opin Endocrinol Diabetes Obes.* 2025;32:279–85. <https://doi.org/10.1097/med.0000000000000934>.
31. Márquez-Cruz M, Kammar-García A, Huerta-Cruz JC, Carrasco-Portugal MdelC, Barranco-Garduño LM, Rodríguez-Silverio J, et al. Three- and six-month efficacy and safety of phentermine in a Mexican obese population. *Int J Clin Pharmacol Ther.* 2021;59:539–48. <https://doi.org/10.5414/cp203943>.
32. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2015;100:342–62. <https://doi.org/10.1210/jc.2014-3415>.
33. Karacabeyli D, Lacaille D. Glucagon-like peptide-1 receptor agonists in arthritis: current insights and future directions. *Nat Rev Rheumatol.* 2025;21:671–83. <https://doi.org/10.1038/s41584-025-01302-0>.
34. Vasireddi N, Hahamyan H, Salata MJ, Karns M, Calcei JG, Voos JE, et al. Emerging use of BPC-157 in orthopaedic sports medicine: a systematic review. *HSS J.* 2025;21:485–95. <https://doi.org/10.1177/15563316251355551>.
35. Lee E, Padgett B. Intra-articular injection of BPC 157 for multiple types of knee pain. *Altern Ther Health Med.* 2021;27:8–13.
36. Yang Y, Cao Y. The impact of VEGF on cancer metastasis and systemic disease. *Semin Cancer Biol.* 2022;86:251–61. <https://doi.org/10.1016/j.semcancer.2022.03.011>.
37. Mead MP, Gumucio JP, Awan TM, Mendias CL, Sugg KB. Pathogenesis and management of tendinopathies in sports medicine. *Transl Sports Med.* 2018;1:5–13. <https://doi.org/10.1002/tsm2.6>.
38. Praet SFE, Ong JH, Purdam C, Welvaert M, Lovell G, Dixon L, et al. Microvascular volume in symptomatic Achilles tendons is associated with VISA-A score. *J Sci Med Sport.* 2018;21:1185–91. <https://doi.org/10.1016/j.jsams.2018.05.013>.
39. Foresta C, Ferlin A, Toni LD, Lana A, Vinanzi C, Galan A, et al. Circulating endothelial progenitor cells and endothelial function after chronic tadalafil treatment in subjects with erectile dysfunction. *Int J Impot Res.* 2006;18:484–8. <https://doi.org/10.1038/sj.ijir.3901465>.
40. Tawfik AM, Radwan MH, Abdulmonem M, Abo-Elenen M, Elgamal SA, Aboufarha MO. Tadalafil monotherapy in management of chronic prostatitis/chronic pelvic pain syndrome: a randomized double-blind placebo controlled clinical trial. *World J Urol.* 2022;40:2505–11. <https://doi.org/10.1007/s00345-022-04074-4>.
41. Teichman SL, Neale A, Lawrence B, Gagnon C, Castaigne J-P, Frohman LA. Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults. *J Clin Endocrinol Metab.* 2006;91:799–805. <https://doi.org/10.1210/jc.2005-1536>.
42. ClinicalTrials.gov. A study to evaluate CJC 1295 in HIV patients with visceral obesity, NCT00267527. <https://clinicaltrials.gov/study/NCT00267527>. Accessed 1 Mar 2026.
43. Gelato MC, Rittmaster RS, Pescovitz OH, Nicoletti MC, Nixon WE, D'Agata R, et al. Growth hormone responses to continuous infusions of growth hormone-releasing hormone. *J Clin Endocrinol Metab.* 1985;61:223–8. <https://doi.org/10.1210/jcem-61-2-223>.
44. Melmed S. Acromegaly pathogenesis and treatment. *J Clin Invest.* 2009;119:3189–202. <https://doi.org/10.1172/jci39375>.
45. Weber AE, Gallo MC, Bolia IK, Cleary EJ, Schroeder TE, Hatch GFR. Anabolic androgenic steroids in orthopaedic surgery: current concepts and clinical applications. *JAAOS Glob Res Rev.* 2022;6:e21.00156. <https://doi.org/10.5435/jaas-global-d-21-00156>.
46. Rodino-Klapac LR, Haidet AM, Kota J, Handy C, Kaspar BK, Mendell JR. Inhibition of myostatin with emphasis on follistatin as a therapy for muscle disease. *Muscle Nerve.* 2009;39:283–96. <https://doi.org/10.1002/mus.21244>.
47. Dueweke JJ, Awan TM, Mendias CL. Regeneration of skeletal muscle after eccentric injury. *J Sport Rehabil.* 2017;26:171–9. <https://doi.org/10.1123/jsr.2016-0107>.
48. Kota J, Handy CR, Haidet AM, Montgomery CL, Eagle A, Rodino-Klapac LR, et al. Follistatin gene delivery enhances muscle growth and strength in nonhuman primates. *Sci Transl Med.* 2009;1:6ra15. <https://doi.org/10.1126/scitranslmed.3000112>.
49. Al-Zaidy SA, Sahenk Z, Rodino-Klapac LR, Kaspar B, Mendell JR. Follistatin gene therapy improves ambulation in Becker muscular dystrophy. *J Neuromuscul Dis.* 2015;2:185–92. <https://doi.org/10.3233/jnd-150083>.
50. Phillips DJ, Jones KL, McGaw DJ, Groome NP, Smolich JJ, Parsson H, et al. Release of activin and follistatin during cardiovascular procedures is largely due to heparin administration. *J Clin Endocrinol Metab.* 2000;85:2411–5. <https://doi.org/10.1210/jcem.85.7.6666>.
51. Bäck S, Dossat A, Parkkinen I, Koivula P, Airavaara M, Richie CT, et al. Neuronal activation stimulates cytomegalovirus promoter-driven transgene expression. *Mol Ther Methods Clin Dev.* 2019;14:180–8. <https://doi.org/10.1016/j.omtm.2019.06.006>.
52. Pickart L, Margolina A. Skin regenerative and anti-cancer actions of copper peptides. *Cosmetics.* 2018;5:29. <https://doi.org/10.3390/cosmetics5020029>.
53. Taylor AA, Tsuji JS, Garry MR, McArdle ME, Goodfellow WL, Adams WJ, et al. Critical review of exposure and effects: implications for setting regulatory health criteria for ingested copper. *Environ Manag.* 2020;65:131–59. <https://doi.org/10.1007/s00267-019-01234-y>.
54. Shen Y, Liu M, Botchway BOA, Zhang Y, Liu X. Molecular mechanisms of cuproptosis in osteoarthritis: pathways, crosstalk, and therapeutic opportunities. *Exp Cell Res.* 2025;453:114800. <https://doi.org/10.1016/j.yexcr.2025.114800>.
55. Ahnfelt-Rønne I, Nowak J, Olsen UB. Do growth hormone-releasing peptides act as ghrelin secretagogues? *Endocrine.* 2001;14:133–5. <https://doi.org/10.1385/endo.14:1.133>.

56. Raun K, Hansen BS, Johansen NL, Thogersen H, Madsen K, Ankersen M, et al. Ipamorelin, the first selective growth hormone secretagogue. *Eur J Endocrinol.* 1998;139:552–61. <https://doi.org/10.1530/eje.0.1390552>.
57. Johansen PB, Nowak J, Skjærbæk C, Flyvbjerg A, Andreassen TT, Wilken M, et al. Ipamorelin, a new growth-hormone-releasing peptide, induces longitudinal bone growth in rats. *Growth Horm IGF Res.* 1999;9:106–13. <https://doi.org/10.1054/ghir.1999.9998>.
58. Prinz P, Stengel A. Control of food intake by gastrointestinal peptides: mechanisms of action and possible modulation in the treatment of obesity. *J Neurogastroenterol Motil.* 2017;23:180–96. <https://doi.org/10.5056/jnm16194>.
59. Mohammadi EN, Louwies T, Pietra C, Northrup SR, Meerveld BG-V. Attenuation of visceral and somatic nociception by ghrelin mimetics. *J Exp Pharmacol.* 2020;12:267–74. <https://doi.org/10.2147/jep.s249747>.
60. Group on behalf of the I 201 S, Beck DE, Sweeney WB, McCarter MD. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients. *Int J Colorectal Dis.* 2014;29:1527–34. <https://doi.org/10.1007/s00384-014-2030-8>.
61. Poher A-L, Tschöp MH, Müller TD. Ghrelin regulation of glucose metabolism. *Peptides.* 2018;100:236–42. <https://doi.org/10.1016/j.peptides.2017.12.015>.
62. Wasko R, Jaskula M, Kotwicka M, Andrusiewicz M, Jankowska A, Liebert W, et al. The expression of ghrelin in somatotroph and other types of pituitary adenomas. *Neuro Endocrinol Lett.* 2008;29:929–38.
63. Bilbao A, Spanagel R. Medical cannabinoids: a pharmacology-based systematic review and meta-analysis for all relevant medical indications. *BMC Med.* 2022;20:259. <https://doi.org/10.1186/s12916-022-02459-1>.
64. Souza MJD, Strock NCA, Ricker EA, Koltun KJ, Barrack M, Joy E, et al. The path towards progress: a critical review to advance the science of the female and male athlete triad and relative energy deficiency in sport. *Sports Med.* 2022;52:13–23. <https://doi.org/10.1007/s40279-021-01568-w>.
65. Lee C, Zeng J, Drew BG, Sallam T, Martin-Montalvo A, Wan J, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell Metab.* 2015;21:443–54. <https://doi.org/10.1016/j.cmet.2015.02.009>.
66. Lyons CL, Roche HM. Nutritional modulation of AMPK-impact upon metabolic-inflammation. *Int J Mol Sci.* 2018;19:3092. <https://doi.org/10.3390/ijms19103092>.
67. Mastrototaro L, Roden M. Insulin resistance and insulin sensitizing agents. *Metabolism.* 2021;125:154892. <https://doi.org/10.1016/j.metabol.2021.154892>.
68. Prakash A, Goa KL. Sermorelin. *BioDrugs.* 1999;12:139–57. <https://doi.org/10.2165/00063030-199912020-00007>.
69. González-Sales M, Barrière O, Tremblay PO, Nekka F, Mamputu J-C, Boudreault S, et al. Population pharmacokinetic and pharmacodynamic analysis of tesamorelin in HIV-infected patients and healthy subjects. *J Pharmacokinetic Pharmacodyn.* 2015;42:287–99. <https://doi.org/10.1007/s10928-015-9416-2>.
70. Ishida J, Saitoh M, Ebner N, Springer J, Anker SD, von Haehling S. Growth hormone secretagogues: history, mechanism of action, and clinical development. *JCSM Rapid Commun.* 2020;3:25–37. <https://doi.org/10.1002/rco2.9>.
71. Vittone J, Blackman MR, Busby-Whitehead J, Tsiao C, Stewart KJ, Tobin J, et al. Effects of single nightly injections of growth hormone-releasing hormone (GHRH 1–29) in healthy elderly men. *Metabolism.* 1997;46:89–96. [https://doi.org/10.1016/s0026-0495\(97\)90174-8](https://doi.org/10.1016/s0026-0495(97)90174-8).
72. Khorram O, Laughlin GA, Yen SSC. Endocrine and metabolic effects of long-term administration of [Nle27]growth hormone-releasing hormone-(1–29)-NH2 in age-advanced men and women. *J Clin Endocrinol Metab.* 1997;82:1472–9. <https://doi.org/10.1210/jcem.82.5.3943>.
73. Falutz J, Allas S, Blot K, Potvin D, Kotler D, Somero M, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. *N Engl J Med.* 2007;357:2359–70. <https://doi.org/10.1056/nejmoa072375>.
74. Makimura H, Feldpausch MN, Rope AM, Hemphill LC, Torriani M, Lee H, et al. Metabolic effects of a growth hormone-releasing factor in obese subjects with reduced growth hormone secretion: a randomized controlled trial. *J Clin Endocrinol Metab.* 2012;97:4769–79. <https://doi.org/10.1210/jc.2012-2794>.
75. Heinemeier KM, Mackey AL, Doessing S, Hansen M, Bayer ML, Nielsen RH, et al. GH/IGF-I axis and matrix adaptation of the musculotendinous tissue to exercise in humans. *Scand J Med Sci Sports.* 2012;22:e1-7. <https://doi.org/10.1111/j.1600-0838.2012.01459.x>.
76. Disser NP, Sugg KB, Talarek JR, Sarver DC, Rourke BJ, Mendias CL. Insulin-like growth factor 1 signaling in tenocytes is required for adult tendon growth. *FASEB J.* 2019;33:12680–95. <https://doi.org/10.1096/fj.201901503r>.
77. Mendias CL, Enselman ERS, Olszewski AM, Gumucio JP, Edon DL, Konnaris MA, et al. The use of recombinant human growth hormone to protect against muscle weakness in patients undergoing anterior cruciate ligament reconstruction: a pilot, randomized placebo-controlled trial. *Am J Sports Med.* 2020;48:1916–28. <https://doi.org/10.1177/0363546520920591>.
78. Bartke A. Growth hormone and aging: updated review. *World J Mens Health.* 2019;37:19–30. <https://doi.org/10.5534/wjmh.180018>.
79. Liao C, Liang X, Zhang X, Li Y. The effects of GLP-1 receptor agonists on visceral fat and liver ectopic fat in an adult population with or without diabetes and nonalcoholic fatty liver disease: a systematic review and meta-analysis. *PLoS ONE.* 2023;18:e0289616. <https://doi.org/10.1371/journal.pone.0289616>.
80. Tung C, Varzideh F, Farroni E, Mone P, Kansakar U, Jankauskas SS, et al. Elamipretide: a review of its structure, mechanism of action, and therapeutic potential. *Int J Mol Sci.* 2025;26:944. <https://doi.org/10.3390/ijms26030944>.
81. Zhao C, Zhuang X, Gao J. Elamipretide: the first cardiolipin-directed mitochondrial therapeutic for Barth syndrome approved under accelerated approval. *Drug Discov Ther.* 2026;19(6):435–6. <https://doi.org/10.5582/ddt.2025.01111>.
82. Zhu Y, Wang H, Fang J, Dai W, Zhou J, Wang X, et al. SS-31 provides neuroprotection by reversing mitochondrial dysfunction after traumatic brain injury. *Oxid Med Cell Longev.* 2018;2018:4783602. <https://doi.org/10.1155/2018/4783602>.
83. Campbell MD, Duan J, Samuelson AT, Gaffrey MJ, Merrihew GE, Egerton JD, et al. Improving mitochondrial function with SS-31 reverses age-related redox stress and improves exercise tolerance in aged mice. *Free Radic Biol Med.* 2019;134:268–81. <https://doi.org/10.1016/j.freeradbiomed.2018.12.031>.
84. Roshanravan B, Liu SZ, Ali AS, Shankland EG, Goss C, Amory JK, et al. In vivo mitochondrial ATP production is improved in older adult skeletal muscle after a single dose of elamipretide in a randomized trial. *PLoS ONE.* 2021;16:e0253849. <https://doi.org/10.1371/journal.pone.0253849>.
85. Low TL, Goldstein AL. Chemical characterization of thymosin beta 4. *J Biol Chem.* 1982;257:1000–6. [https://doi.org/10.1016/s0021-9258\(19\)68299-2](https://doi.org/10.1016/s0021-9258(19)68299-2).
86. Sosne G, Qiu P, Goldstein AL, Wheeler M. Biological activities of thymosin β 4 defined by active sites in short peptide

- sequences. *FASEB J*. 2010;24:2144–51. <https://doi.org/10.1096/fj.09-142307>.
87. Goldstein AL, Hannappel E, Sosne G, Kleinman HK. Thymosin β 4: a multi-functional regenerative peptide. Basic properties and clinical applications. *Expert Opin Biol Ther*. 2012;12:37–51. <https://doi.org/10.1517/14712598.2012.634793>.
 88. Treadwell T, Kleinman HK, Crockford D, Hardy MA, Guarnera GT, Goldstein AL. The regenerative peptide thymosin β 4 accelerates the rate of dermal healing in preclinical animal models and in patients. *Ann N Y Acad Sci*. 2012;1270:37–44. <https://doi.org/10.1111/j.1749-6632.2012.06717.x>.
 89. Spurney CF, Cha H-J, Sali A, Pandey GS, Pistilli E, Guerron AD, et al. Evaluation of skeletal and cardiac muscle function after chronic administration of thymosin β -4 in the dystrophin deficient mouse. *PLoS ONE*. 2010;5:e8976. <https://doi.org/10.1371/journal.pone.0008976>.
 90. Ruff D, Crockford D, Girardi G, Zhang Y. A randomized, placebo-controlled, single and multiple dose study of intravenous thymosin β 4 in healthy volunteers. *Ann N Y Acad Sci*. 2010;1194:223–9. <https://doi.org/10.1111/j.1749-6632.2010.05474.x>.
 91. Wang X, Liu L, Qi L, Lei C, Li P, Wang Y, et al. A first-in-human, randomized, double-blind, single- and multiple-dose, phase I study of recombinant human thymosin β 4 in healthy Chinese volunteers. *J Cell Mol Med*. 2021;25:8222–8. <https://doi.org/10.1111/jcmm.16693>.
 92. Sosne G, Kleinman HK, Springs C, Gross RH, Sung J, Kang S. 0.1% RGN-259 (thymosin β 4) ophthalmic solution promotes healing and improves comfort in neurotrophic keratopathy patients in a randomized, placebo-controlled, double-masked phase III clinical trial. *Int J Mol Sci*. 2022;24:554. <https://doi.org/10.3390/ijms24010554>.
 93. Zhang Y, Dong Q, Bian X, Qiao Z, Cui C, Yang N, et al. Recombinant human thymosin beta 4 improves ischemic cardiac dysfunction in mice and patients with acute ST-segment elevation myocardial infarction after reperfusion. *Cardiovasc Res*. 2025;121:2747–58. <https://doi.org/10.1093/cvr/cvaf223>.
 94. Di H, Huang J, Zhang D, Ni F, Zheng R, Geng H. Thymosin beta 4: an emerging therapeutic candidate for kidney diseases. *Peptides*. 2026;195:171467. <https://doi.org/10.1016/j.peptides.2026.171467>.
 95. Sribenja S, Wongkham S, Wongkham C, Yao Q, Chen C. Roles and mechanisms of β -thymosins in cell migration and cancer metastasis: an update. *Cancer Investig*. 2013;31:103–10. <https://doi.org/10.3109/07357907.2012.756111>.
 96. Benedetti F. Placebo and the new physiology of the doctor-patient relationship. *Physiol Rev*. 2013;93:1207–46. <https://doi.org/10.1152/physrev.00043.2012>.
 97. Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta J-K. Neurobiological mechanisms of the placebo effect. *J Neurosci*. 2005;25:10390–402. <https://doi.org/10.1523/jneurosci.3458-05.2005>.
 98. Voon V, Fernagut P-O, Wickens J, Baunez C, Rodriguez M, Pavon N, et al. Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. *Lancet Neurol*. 2009;8:1140–9. [https://doi.org/10.1016/s1474-4422\(09\)70287-x](https://doi.org/10.1016/s1474-4422(09)70287-x).
 99. Smits RM, Veldhuijzen DS, Wulffraat NM, Evers AWM. The role of placebo effects in immune-related conditions: mechanisms and clinical considerations. *Expert Rev Clin Immunol*. 2018;14:761–70. <https://doi.org/10.1080/1744666x.2018.1516144>.
 100. van Lennep J (Hans)PA, Trossèl F, Perez RSGM, Otten RHJ, van Middendorp H, Evers AWM, et al. Placebo effects in low back pain: A systematic review and meta-analysis of the literature. *Eur J Pain*. 2021;25:1876–97. <https://doi.org/10.1002/ejp.1811>.
 101. Saueressig T, Owen PJ, Pedder H, Tagliaferri S, Kaczorowski S, Altrichter A, et al. The importance of context (placebo effects) in conservative interventions for musculoskeletal pain: a systematic review and meta-analysis of randomized controlled trials. *Eur J Pain*. 2024;28:675–704. <https://doi.org/10.1002/ejp.2222>.
 102. Valero F, González-Mohino F, Salinero JJ. Belief that caffeine ingestion improves performance in a 6-minute time trial test without affecting pacing strategy. *Nutrients*. 2024;16:327. <https://doi.org/10.3390/nu16020327>.
 103. Pollo A, Carlino E, Benedetti F. The top-down influence of ergogenic placebos on muscle work and fatigue. *Eur J Neurosci*. 2008;28:379–88. <https://doi.org/10.1111/j.1460-9568.2008.06344.x>.
 104. Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I. Open-label placebo treatment in chronic low back pain. *Pain*. 2016;157:2766–72. <https://doi.org/10.1097/j.pain.0000000000000700>.
 105. González-Bailón S, Lelkes Y. Do social media undermine social cohesion? A critical review. *Soc Issues Policy Rev*. 2023;17:155–80. <https://doi.org/10.1111/sipr.12091>.
 106. Zamil DH, Ameri M, Fu S, Abughosh FM, Katta R. Skin, hair, and nail supplements advertised on Instagram. *Baylor Univ Med Cent Proc*. 2023;36:38–40. <https://doi.org/10.1080/08998280.2022.2124767>.
 107. Ricke J-N, Seifert R. Disinformation on dietary supplements by German influencers on Instagram. *Naunyn Schmiedeberg's Arch Pharmacol*. 2025;398:5629–47. <https://doi.org/10.1007/s00210-024-03616-4>.
 108. Chou W-YS, Gaysynsky A, Trivedi N, Vanderpool RC. Using social media for health: National data from HINTS 2019. *J Health Commun*. 2021;26:184–93. <https://doi.org/10.1080/10810730.2021.1903627>.
 109. Kraljevic S, Stambrook PJ, Pavelic K. Accelerating drug discovery. *EMBO Rep*. 2004;5:837–42. <https://doi.org/10.1038/sj.embor.7400236>.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.