Review

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Review

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

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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 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), 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 is scarce, and there is potential for serious harm. This narrative review focuses on peptide utilization in sports medicine and alternative treatments for specific peptides. 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.

Keywords: peptide; athletic performance; AOD-9604; BPC-157; sermorelin; tesamorelin; CJC-1295; MOTS-C; ipamorelin; thymosin beta-4; TB-500

1. Introduction

Peptides are short chains of up to 40 to 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-1RA) tirzepatide and semaglutide, which have revolutionized weight loss and diabetes care [2]. Parathyroid hormone 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 USD 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 marketed to athletes and the general public [4]. The purported benefits of these substances include accelerated musculoskeletal injury recovery, muscle hypertrophy, athletic performance

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enhancement, and many others [4]. As peptides produced on the gray market are not subject to 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 the sports medicine community. On one hand, preclinical data for many peptides show compelling improvements 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]. 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) will 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 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 synthesized through one of three methodologies: solid-phase peptide synthesis, liquid-phase peptide synthesis, or a hybrid approach [2,9]. 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 [2,9,10]. Substitutions or deletions in amino acid residues can result in a peptide with vastly different biological properties, behaving in an unpredictable or dangerous manner [11]. 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 [2,10]. 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 [10,12,13]. Therefore, the lack of regulatory oversight of grey market peptides carries potentially 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 US is regulated under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act [14]. 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 [15]. 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 [15]. 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 [16] . 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 [17]. Australia regulates compounding under the auspices of the Therapeutic Goods Administration (TGA) [18], which generally allows the compounding of peptides entered on the Australian Register of Therapeutic Goods (ARTG) [18].

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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. Analysis of Google search trends were conducted to identify peptides most commonly searched for from 2024 onward (Figure 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 (Figure 1). This was preceded by searches for approved peptides such as "Tirzepatide" and "Semaglutide" (Figure 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" (Figure 1). Many popular peptides relevant to sports medicine are discussed in the following sections and are also summarized in Supplemental 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 [19–22] offer evidence-based alternatives to peptides with purported musculoskeletal uses.

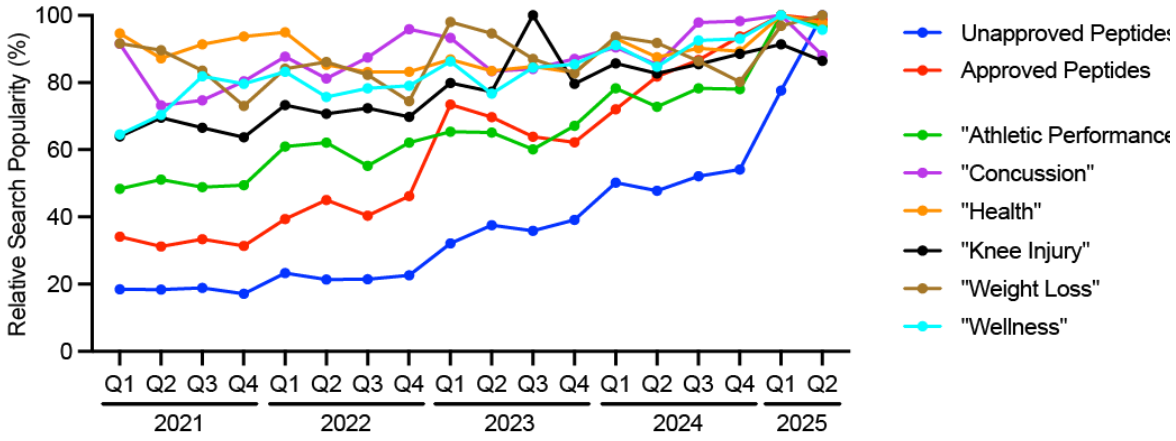

Figure 1. Google search trend analysis from Q1 2022 through Q2 2025 demonstrating the relative global popularity of search terms or sets of terms. Unapproved Peptides consist of the following terms which were analyzed a single relative set: "AOD-9604", "BPC-157", "CJC-1295", "Follistatin", "GHK-Cu", "Ipamorelin", "MOTS-C", and "TB-500". Approved Peptides consist of the following terms which 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.

3.1. AOD-9604

AOD-9604 (Anti-Obesity Drug 9604) is a peptide fragment of residues 177-191 of human growth hormone (hGH), with a tyrosine residue added to enhance stability [23]. AOD-9604 was originally developed to isolate the lipolytic properties of hGH while avoiding anabolic and insulin-desensitizing effects [23,24]. AOD-9604 is proposed to stimulate lipolysis through interaction with beta adrenergic receptors [23–25]. 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 chronic hGH administration [23–25]. AOD-9604 significantly reduced fat mass in rodent models of obesity [25], which then led to six randomized, double-blind, placebo-controlled trials involving over 900 patients to evaluate the treatment of obesity [24]. The safety

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profile was favorable, with no changes in IGF-1 or insulin sensitivity [24]. 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 [26].

Recently, there has been interest in AOD-9604 for cartilage repair based on promising results in a rabbit model of osteoarthritis [27], but there is 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 [28]. Alternatives to AOD-9604 for weight loss include the GLP-1RAs, or the norepinephrine and dopamine releasing agent phentermine [29–31].

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 [32]. 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 [32,33]. Preclinical data demonstrates BPC-157 can potentially be effective in healing musculoskeletal injuries [33], 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 [6]. 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.

A major concern about the safety of BPC-157 stems from its role in stimulating angiogenesis via VEGF. High VEGF abundance in tumor tissue or blood is consistently associated with worse outcomes in cancer treatment [34]. Additionally, while vascularization may improve healing in some tissues, neovascularization is correlated with worse functional outcomes in chronic tendinopathy [35,36]. A safer, evidence-based alternative to BPC-157 for improving vascular function is the tadalafil, which improves vascular function through increasing circulating endothelial progenitor cells, enhancing flow-mediated dilation, promoting angiogenesis, and augmenting tissue perfusion [37]. For arthralgias, emerging data indicates GLP-1RAs appear to reduce joint pain and inflammation through a combination of direct weight loss as well as intraarticular anti-inflammatory and chondroprotective effects [38].

3.3 CJC-1295

CJC-1295 is a synthetic analogue of Growth Hormone-Releasing Hormone (GHRH) and has a significantly extended half-life compared to endogenous GHRH [39]. 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, with a 2-10 fold increase in hGH for 6 days or more post-injection [39]. 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 placebo group reported similar events [39]. These side effects included injection site reaction, headache, diarrhea, and systemic vasodilatory responses [39]. 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 [40].

Social media influencers have promoted the use of CJC-1295 to enhance muscle mass, reduce fat, and improve tissue healing. CJC-1295 is sometimes combined with ipamorelin to try to maximize hGH pulse amplitude while attempting to mitigate continuous GHRH stimulation issues. The continuous elevation of hGH can cause pituitary desensitization and blunting of the natural hGH axis [41]. Persistent activation of the hGH-IGF-1 axis can cause insulin resistance, water retention, and organomegaly [42]. Safer and likely more effective treatment options to CJC-1295 for body fat reduction include GLP-1RAs or phentermine [29–31]. For increasing muscle mass in certain patients with sarcopenia, low dose testosterone may be appropriate [43] .

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3.4 FS-344

Follistatin is a naturally occurring autocrine glycoprotein. The 344 isoform (FS-344) is an alternatively spliced peptide which inhibits myostatin and activin signaling [44]. Myostatin and activin induce muscle atrophy, and by sequestering inhibitors of atrophy, FS-344 is posited to increase muscle mass and strength [44,45]. FS-344 has gained traction in the gray market due to its potential ability to induce muscle hypertrophy.

Adeno-associated viral (AAV) gene-mediated delivery of FS-344 has shown dramatic increases in muscle mass and strength in mouse and non-human primate models [7,46]. A small clinical trial in Becker Muscular Dystrophy patients showed safety and functional improvements with FS-344 AAV gene therapy [47]. An important distinguishing factor between gene therapy and injectable FS-344 has to do with the relatively short one-to-two hour half-life of follistatin [48]. The gene vector that produces FS-344 utilizes the cytomegalovirus (CMV) promoter, which is a constitutively active promoter [49], 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 include low-dose testosterone, which may be able to safely and effectively increase muscle mass in appropriate patients [43].

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 [50], topical GHK-Cu promotes collagen synthesis, stimulates angiogenesis, and possesses antioxidant and anti-inflammatory properties through cytokine downregulation [50]. In humans, GHK-Cu is widely used in cosmetics to improve skin texture and composition [50]. In the US, Europe, and Australia, GHK-Cu is not approved as a drug for topical use but is allowed as a cosmetic product due 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 [50], injectable forms pose distinct risks. When taken orally, the peptide component of GHK-Cu would likely undergo rapid proteolytic degradation in the gastrointestinal tract, releasing free copper ions. This effectively converts GHK-Cu into an oral copper supplement rather than delivering the intact peptide complex systemically. Ingesting high levels of soluble copper salts can cause GI and liver toxicity [51]. Within the joint, excess copper promotes aggregation of lipoylated tricarboxylic acid cycle enzymes and destabilization of iron-sulfur clusters, thereby impairing mitochondrial integrity leading to chondrocyte death [52]. No direct approved alternative medications are available for promoting joint healing, although GLP-1RAs appear to be effective in treating joint pain [38].

3.6 Ipamorelin

Ipamorelin is a pentapeptide and a selective agonist of the ghrelin/growth hormone secretagogue receptor (GHSR1) that stimulates the pituitary gland to release hGH in a pulsatile manner [53]. Unlike other GHSR1 agonists, ipamorelin does not significantly stimulate the release of cortisol or prolactin [54]. Animal studies demonstrate ipamorelin may function similar to other hGH secretagogues as it relates to musculoskeletal effects [55]. However, unlike other hGH secretagogues, ipamorelin appears to stimulate food intake and adiposity through activation of the ghrelin receptor [56]. Activation of the ghrelin receptor also appears to reduce colonic hypersensitivity, and visceral and somatic allodynia [57]. 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 [58]. Ipamorelin also has been marketed on social media as an

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orexigenic agent to aid individuals consuming high protein diets overcome the satiety-inducing effects of protein.

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 [59]. 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 GHSR activation could contribute to somatotroph hyperplasia or adenoma formation [60]. 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 like dronabinol that can increase appetite [61,62].

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 acts as an exercise mimetic, interacting with the folate cycle and AMPK pathways to regulate glucose metabolism and insulin sensitivity [5,63]. 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 [5,63]. Human data is limited to observational studies correlating endogenous MOTS-c levels with insulin sensitivity [5,63], 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 [64]. Safe and effective alternatives to MOTS-c for weight loss include the GLP-1RAs or phentermine [29,30]. For improving insulin sensitivity there are a variety of alternatives, including metformin, thiazolidinediones, sodium-glucose transport protein 2 (SGLT2) inhibitors, and GLP-1RAs [65].

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 [66]. 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 trans-3-hexenoic acid group, which increases the half-life and potency of hGH axis stimulation [67,68]. While not approved by the EMA 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 [68]. These peptides are potentially safer than exogenous hGH because they preserve feedback control of both GH and IGF-1 and protect against imbalances between GH and IGF-1 levels [68]. Much of the research on sermorelin and tesamorelin have focused on changes in body composition. A 5-month treatment course of sermorelin increased lean body mass by 2.3% in men, with no change in fat mass [69]. In HIV+ individuals 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 [70]. 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 [71].

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

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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 [72–74]. hGH promotes slow-wave sleep, which is the sleep cycle phase that is crucial for physical recovery and cognitive function [75]. hGH has been proposed to have anti-aging effects, although this is controversial [76]. While short term use of hGH appears to offer therapeutic benefits for some conditions [68], in the long term organisms with sustained elevations in hGH over several years typically have shorter lifespans [76]. Alternatives to the use of sermorelin or tesamorelin for visceral fat reduction include the GLP-1RAs and phentermine [30,77].

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 [78]. SS-31 underwent rigorous development and was recently approved by the FDA for Barth Syndrome [79], with EMA 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 [78]. SS-31 is generally well-tolerated with no major side effects [78]. Additionally, preclinical studies demonstrate that SS-31 improves cognitive function in traumatic brain injuries [80], 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 [79], 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 [81]. In humans, a single 2-hour infusion of elamipretide acutely improved mitochondrial ATP production capacity in skeletal muscle, but this did not translate to reduced muscle fatiguability [82]. SS-31 is relatively unique in its class, and no currently approved drugs function in a similar manner.

3.10 Thymosin Beta-4 and TB-500

Thymosin Beta-4 (Tβ4) is a 43-amino acid peptide that functions as a G-actin sequestering molecule [83]. TB-500 is a synthetic 7-amino acid peptide corresponding to amino acids 17-23 of Tβ4, which represents the central actin-binding domain that has cell migration and wound healing [84]. Tβ4 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, Tβ4 is released by platelets, macrophages, and other immune cells to initiate the repair cascade [85]. In preclinical models, Tβ4 has demonstrated broad regenerative effects across multiple tissue types. Tβ4 accelerated healing of full-thickness dermal wounds in normal, diabetic, steroid-treated, and aged mice, with reduced scarring and improved collagen organization [86]. In skeletal muscle injury models, Tβ4 acted as a chemoattractant for muscle stem cells and increased regenerating muscle fibers, though this did not translate to improvements in strength [87]. Clinical trials focused on safety have generally found short term use of Tβ4 to be safe, with similar adverse event profiles between placebo and drug treated groups [88,89]. An ophthalmic formulation of Tβ4 has been studied in small clinical trials of a rare corneal disease, neurotrophic keratopathy, and Tβ4 applied to the surface of the cornea appears to be safe and effective [90]. A clinical trial evaluating Tβ4 in myocardial infarctions was shown to be safe, with mixed results on efficacy for infarct size [91].

The purported use of Tβ4 and TB-500 on social media often centers around injury recovery and metabolic substrate restoration after endurance exercise, but human data is lacking. While there is some encouraging preclinical data, there are no indications of the clinical efficacy of Tβ4 or TB-500

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for safely improving musculoskeletal repair or athletic performance. There are also significant safety concerns about the use of these peptides. Tβ4 is overexpressed in multiple tumor types, including colorectal, pancreatic, breast, and lung cancers, and elevated Tβ4 levels correlate with tumor progression, metastasis, and poor prognosis [92]. Tβ4 promotes epithelial-mesenchymal transition (EMT), a process critical for cancer metastasis, and enhances tumor angiogenesis through the same mechanisms that promote wound healing [93]. While a causal role for exogenous Tβ4 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 Tβ4 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. The 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 [94]. Related to this, the contextual effect of therapy is a complex psychobiological 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 [94]. Contextual effects can result in robust physiological changes, even though the compound that is being consumed has no direct pharmacologic mechanism of action [94]. When the compound does have a pharmacological mechanism of action, contextual effects can modulate the efficacy of the therapeutic intervention [94].

Peptides constitute near ideal factors for amplified contextual effects because they often combine high expectancy, invasive injections, 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 [95]. 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 [95]. Dopaminergic activation can contribute to polypharmacy [96], 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 [97].

Contextual effects appear to have small to moderate effects on musculoskeletal pain and athletic performance [98–101]. 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 [102]. The manner in which contemporary social media platforms reinforce interest [103] 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 [103] 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 [104,105]. 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 [106], so it is likely that contextual effects around peptides will continue to grow, making informed decisions with providers about evidence-based peptide even more important (Figure 2). Additionally, potential positive effects of the peptide need to be weighed against potential negative effects, such as cancer metastasis or mortality.

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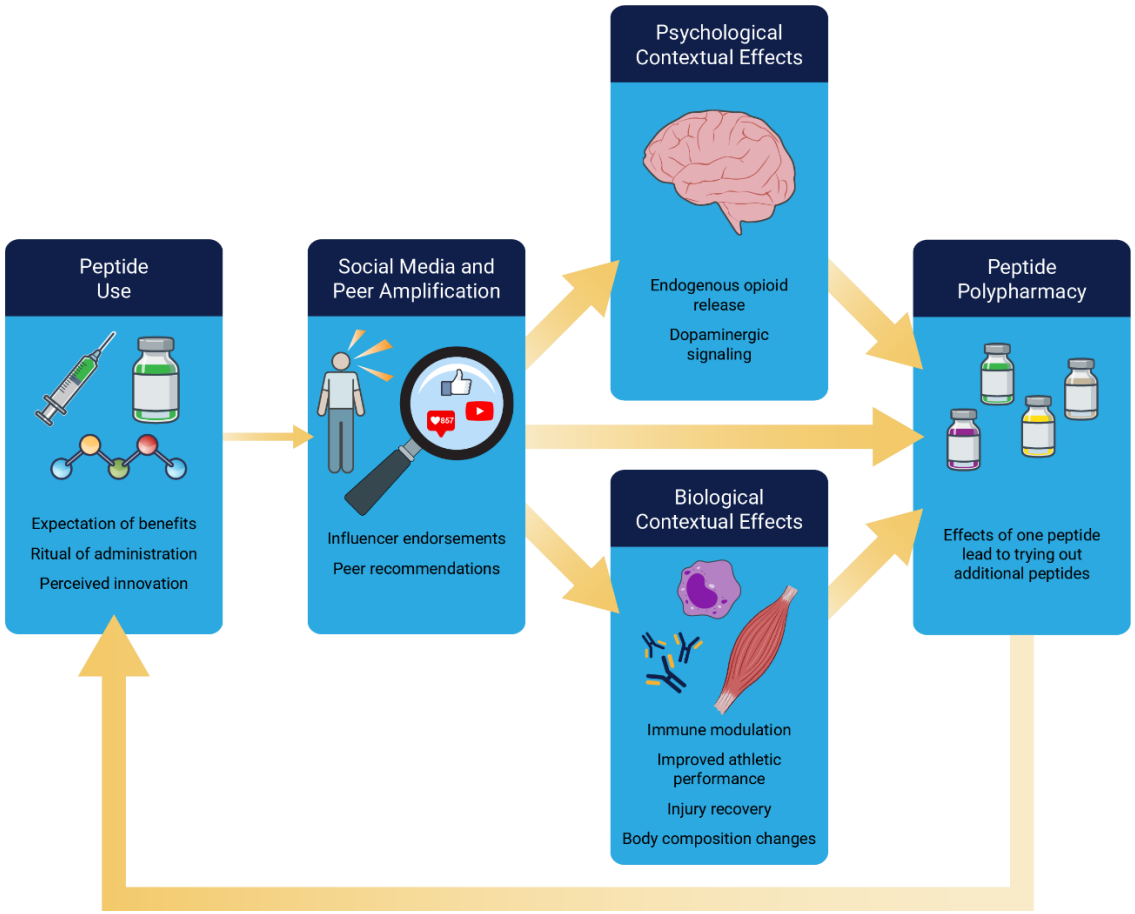

Figure 2. Proposed model of the reinforcing cycle of social media and peer amplification leading to placebo and contextual effects. Illustration of how peptide use is influenced by factors like expectations and rituals, and is further amplified by social media and peer endorsements. These trigger psychological 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.

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 enhancement, 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 Figure 3. We review additional discussion points in Supplemental Material 1.

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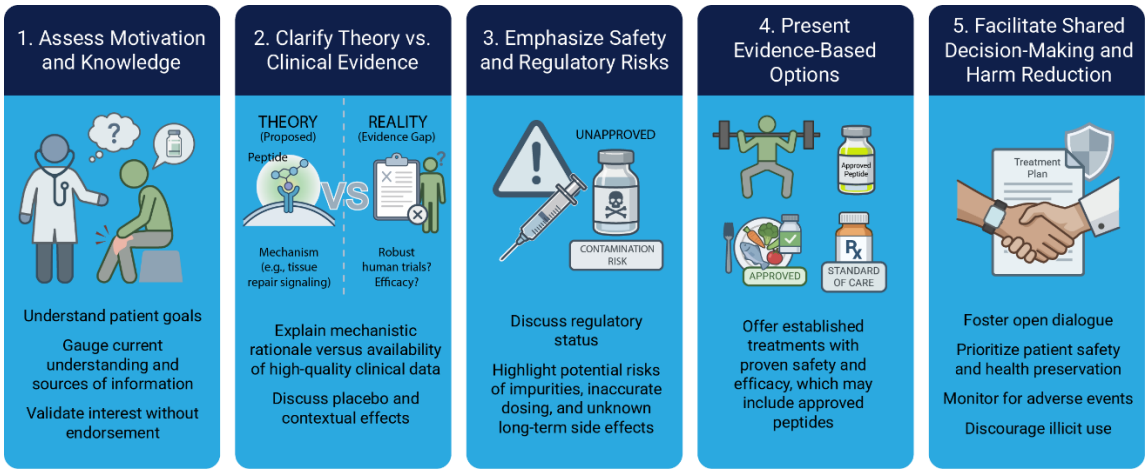

Figure 3. Discussing peptides with patients. A five-step theoretical framework for clinicians to discuss peptides with patients.

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 Tβ4 demonstrate impressive healing properties in animals, the translation to humans is stalled by a lack of rigorous, controlled trials. Of 5,000 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 [107]. Future progress depends on moving peptides out of the gray market and into the transparent light of pharmaceutical development (Figure 4). Until high-quality data emerges 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 (Figure 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.

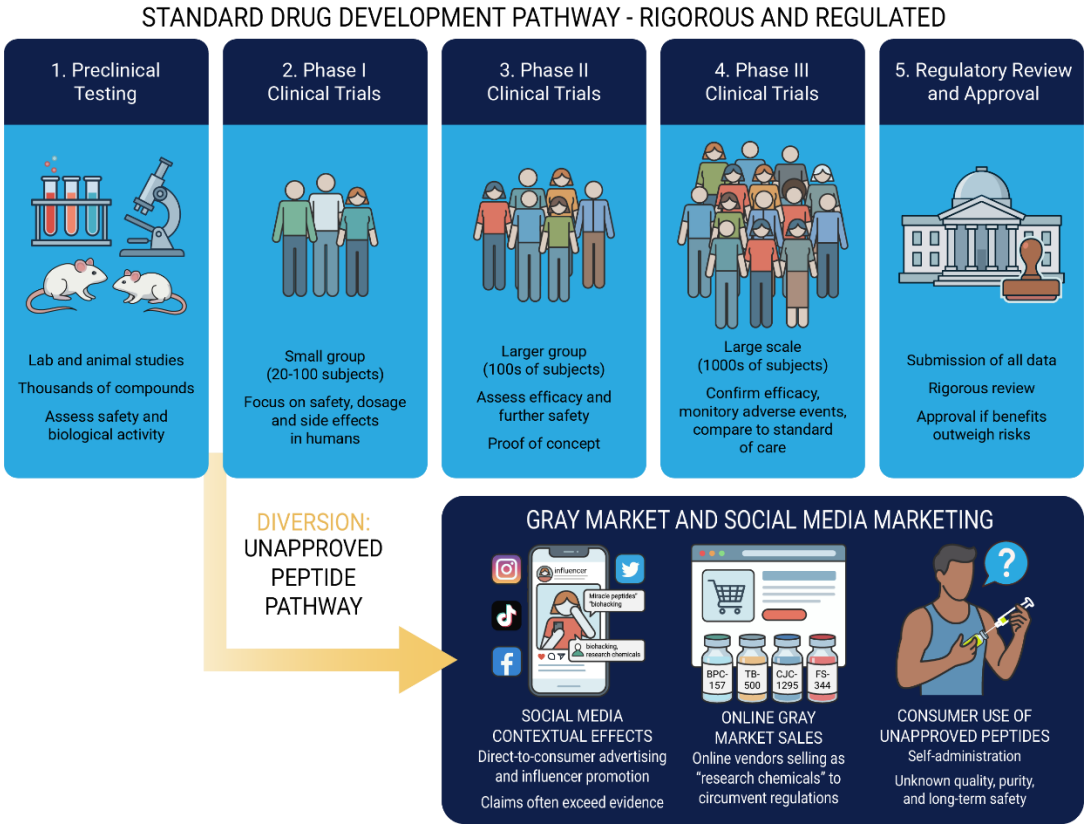

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Figure 4. Standard drug development pathway compared with gray market distribution of unapproved peptides. The regulatory process for drugs approval is shown in the upper panel. The lower pathway illustrates diversion of peptides into an unapproved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

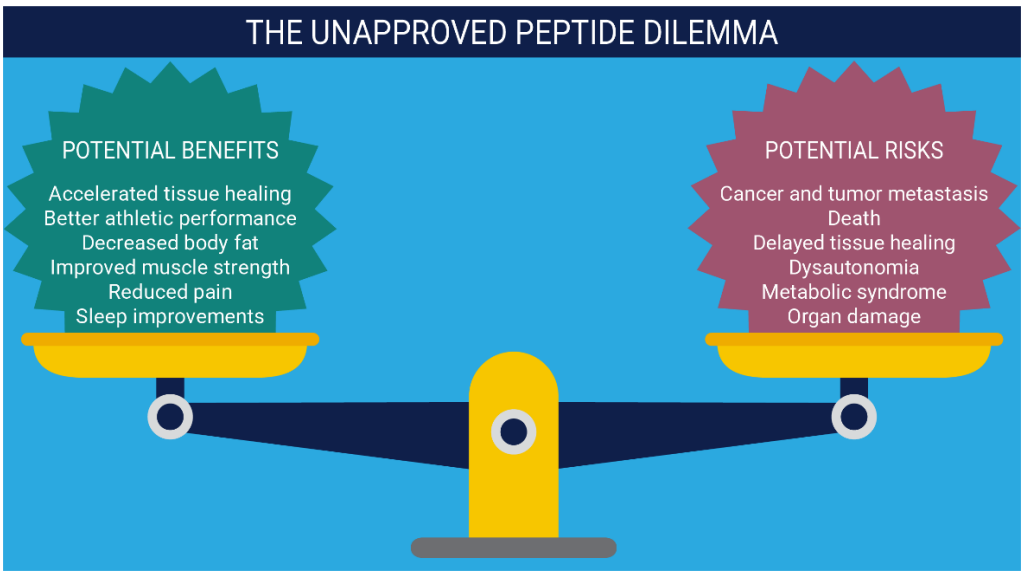

Figure 5. Overview of the unapproved peptide dilemma. The potential benefits and risks of unapproved peptides.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Supplemental Table 1: Summary of peptides discussed in this manuscript. Supplemental Material 1: Additional talking points around the safe use of peptides.

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Abbreviations

The following abbreviations are used in this manuscript:

AAV	Adeno-associated virus
AOD-9604	Anti obesity drug 9604
ARTG	Australian Register of Therapeutic Goods
BMAC	Bone marrow aspirate concentrate
BPC-157	Body protection compound 157

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cGMP	Current good manufacturing practice
CMV	Cytomegalovirus
EMA	European Medicines Agency
ESWT	Extracorporeal shock wave therapy
FDA	U.S. Food and Drug Administration
FS-344	Follistatin 344
GHK-Cu	Glycyl L histidyl L lysine copper (copper peptide complex)
GHRH	Growth hormone releasing hormone
GHSR1	Ghrelin/growth hormone secretagogue receptor 1
GLP-1RA	Glucagon like peptide 1 receptor agonist
hGH	Human growth hormone
HIV	Human immunodeficiency virus
IGF-1	Insulin like growth factor 1
MOTS-c	Mitochondrial ORF of the 12S rRNA type c
PDE5	Phosphodiesterase type 5
PPP	Platelet poor plasma
PRP	Platelet rich plasma
PTH	Parathyroid hormone
SS-31	Elamipretide
SVF	Stromovascular fraction (of adipose tissue)
Tβ4	Thymosin Beta-4
TB-500	Thymosin beta 4 fragment
TGA	Therapeutic Goods Administration (Australia)
USP	United States Pharmacopeia
VEGF	Vascular endothelial growth factor

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