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MINI REVIEW

The microgram hypothesis: a translational dosing error in Epitalon peptide research and its implications for human aging application

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Abstract

Epitalon (Ala-Glu-Asp-Gly), a synthetic tetrapeptide derived from the pineal gland, has attracted considerable attention in anti-aging research for its capacity to activate telomerase, restore circadian melatonin secretion, and extend lifespan across multiple species. The standard dosing convention in the longevity community, typically 5 to 10 mg per day administered subcutaneously, has persisted for over two decades without rigorous translational justification. This paper presents a hypothesis-generating translational re-examination of the preclinical and clinical evidence and identifies a fundamental translational error underlying current dosing practice. Through comparative potency analysis, we demonstrate that the 5 to 10 mg human dosing paradigm originates from studies conducted with Epithalamin, a crude polypeptide extract of bovine pineal glands, rather than with Epitalon itself. Primate data comparing both compounds reveal a model- and endpoint-specific potency differential of approximately 500-fold, while *Drosophila* models suggest a comparable, model-specific 1,000-fold differential in antioxidant efficacy. Allometric scaling of the effective murine treatment-day dose (1.0 µg per mouse, administered subcutaneously on 5 consecutive days each month) yields a per-treatment-day Human Equivalent dose of approximately 190 to 230 µg for a 70-kg individual. Furthermore, recent *in vitro* data demonstrate a non-monotonic concentration-response pattern in the BT474 breast cancer cell line, with peak telomere elongation at 0.2 µg/mL and declining effects at higher concentrations. Taken together, these findings support the testable translational hypothesis that Epitalon should be evaluated in the low microgram range, approximately 100 to 300 µg per treatment day, with treatment schedule and frequency to be defined in formal dose-finding studies, rather than the milligram range currently employed. The current practice may represent systematic overdosing rooted in the historical conflation of a crude extract with a purified synthetic peptide.

Keywords: Epitalon, Epithalamin, dosing error, allometric scaling, peptide bioregulator, geroprotection

Introduction

The pineal gland has long occupied a central position in neuroendocrine theories of aging. Its principal secretory product, melatonin, declines predictably with age, and this decline has been implicated in the deterioration of circadian regulation, immune competence, and antioxidant defense [1]. Beginning in the early 1970s, researchers at the St. Petersburg Institute of Bioregulation and Gerontology pursued the isolation of low-molecular-weight peptides from the pineal gland, culminating in the development of Epithalamin, a pharmacopoeial extract from bovine pineal tissue, and subsequently Epitalon (Ala-Glu-Asp-Gly), a synthetic tetrapeptide designed to replicate the active fraction of that extract [2].

Over the past 25 years, Epitalon has accumulated a substantial body of preclinical evidence spanning cell culture, *Drosophila*, rodent, and primate models. Its reported effects include the activation of telomerase and elongation of telomeres in human somatic cells [3], the restoration of nocturnal melatonin secretion in aged primates [4], the suppression of spontaneous and chemically induced carcinogenesis in rodents [5, 6], and the extension of lifespan across multiple species [7, 8]. In human clinical trials, pineal peptide preparations have been associated with

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reduced mortality, improved cardiovascular indices, and normalized immune and endocrine parameters in elderly cohorts followed for up to eight years [9].

Despite this breadth of investigation, a critical gap has persisted in the translational pharmacology of this compound. The dosing conventions adopted by researchers, clinicians, and the broader anti-aging community have remained remarkably static, centering on 5 to 10 mg per day administered subcutaneously for courses of 10 to 20 days. This dosing range, however, was never established through formal dose-finding studies with the synthetic peptide Epitalon. Instead, it derives directly from the clinical protocols developed for Epithalamin, the crude pineal extract, which is a fundamentally different preparation with distinct pharmacological properties.

In addition to the dose ranges reported in the formal scientific literature, real-world dosing in the longevity and biohacking community varies substantially. Protocols promoted by clinics, content creators, and online vendors range from low-dose regimens (1–2 mg/day, sometimes for extended cycles of 20–30 days) and moderate-dose regimens (5 mg/day or 5 mg twice daily, 10–20 days; the most frequently cited range), to higher-dose regimens (10 mg once or twice daily) and largely anecdotal experimental ranges (≥ 20 mg/day). The persistence and breadth of this milligram-range practice, in the absence of formal human dose-finding data, motivates the present analysis.

The present paper examines the origins of this translational error, synthesizes evidence from comparative potency analyses across multiple biological models, applies allometric scaling to derive a provisional human equivalent dose, and integrates recent *in vitro* data demonstrating a non-linear dose-response relationship. As a hypothesis-generating translational mini-review, the paper proposes that the appropriate human dose range for Epitalon may lie approximately one to two orders of magnitude below current convention, in the microgram rather than the milligram range, and that this hypothesis warrants formal clinical evaluation through structured dose-finding studies.

Methodology

This review was designed as a structured, hypothesis-generating narrative synthesis. In contrast to a formal systematic review, the objective was not the exhaustive inclusion of all available studies but the identification and critical integration of evidence directly relevant to the translational dosing question for Epitalon. The methodological approach combines a transparent literature synthesis with targeted comparative and translational analyses, comprising three complementary components: literature search and study selection, comparative potency analysis, and allometric dose translation.

Literature search and study selection

PubMed/MEDLINE, Web of Science, and Google Scholar were searched from database inception through 31 December 2025. Searches were conducted without language restrictions at the initial screening stage. Search terms included Epitalon, Epithalamin, epithalon, AEDG tetrapeptide, pineal peptide, Khavinson, telomerase, melatonin secretion, aging, lifespan extension peptide, dose-response peptide, allometric scaling peptide, and human equivalent dose. Terms were combined using Boolean operators and adapted to the syntax of each database. The following exemplary PubMed search string illustrates the applied logic: ("Epitalon" OR "Epithalamin" OR "epithalon" OR "AEDG" OR "pineal tetrapeptide" OR "Khavinson") AND ("telomerase" OR "melatonin" OR "lifespan" OR "aging" OR "dose-response" OR "potency" OR "allometric scaling" OR "human equivalent dose")

The database search was supplemented by backward citation screening of all eligible primary studies and forward citation tracking of key foundational papers.

Screening and full-text eligibility assessment were performed by a single reviewer using prespecified criteria. Records were first assessed at the title and abstract level; those meeting eligibility criteria or requiring further clarification were retrieved for full-text assessment. Studies were eligible if they: (1) reported biological activity data for Epitalon or Epithalamin; (2) included a direct or derivable comparison of the two compounds, for example through shared endpoints or comparable experimental systems; (3) reported quantitative dose-response data relevant to the translational argument; or (4) addressed the historical context of dosing conventions. Studies were excluded if the active compound could not be identified with confidence, if no relevant endpoint was reported, or if the paper represented a duplicate publication without methodological additions. In cases of ambiguity regarding the specific compound utilized, the study was conservatively excluded.

Non-English full texts were retained when sufficient information was available from English abstracts, translated sections, or bilingual bibliographic records to identify the compound, dosing regimen, experimental model, and quantitative endpoint.

Greater interpretive weight was assigned to studies that:

(i) directly compared Epithalamin and Epitalon under matched experimental conditions (*e.g.*, Goncharova *et al*. [10], comparing both compounds in aged rhesus macaques).

(ii) reported quantitative dose-response relationships (*e.g.*, Al-dulaimi *et al*. [11], reporting telomere length across the 0.1–1.0 μg/mL range in human cell lines).

(iii) allowed extraction of dosing information directly relevant to translational scaling (*e.g.*, Anisimov *et al*. [8], specifying the effective murine treatment-day dose in absolute terms).

Narrative reports and studies lacking compound-specific dose information were given correspondingly less interpretive weight in the synthesis. No formal risk-of-bias assessment was performed, as the objective was conceptual synthesis and translational hypothesis development rather than a formal systematic review.

Results of the search

The search identified 247 records in PubMed/MEDLINE, 114 in Web of Science, and the first 200 Google Scholar records sorted by relevance. After removal of duplicates, 385 unique records were screened at the title and abstract level, of which 72 were retrieved for full-text assessment. An additional 11 records were identified through citation tracking and retrieved for full-text assessment. Of the 83 full texts assessed for eligibility, 68 were excluded because the compound used could not be clearly identified (n = 28), no relevant quantitative endpoint was reported (n = 22), or the paper represented a duplicate publication without methodological additions (n = 18). Fifteen studies, published between 2002 and 2025, met the eligibility criteria and were included in the final synthesis; additional sources were cited where needed for methodological or contextual background.

Comparative potency analysis

A comparative potency analysis was performed using data from studies in which both preparations were tested under closely matched experimental conditions in the same biological model. The principal comparison derived from a primate study in which Epithalamin (5 mg/animal/day) and Epitalon (10 μg/animal/day) were administered to aged female rhesus macaques, with nocturnal melatonin concentration serving as the functional endpoint [10]. Supplementary potency comparisons were drawn from *Drosophila melanogaster* experiments in which Epitalon demonstrated superior antioxidant efficacy at doses 1,000-fold lower than Epithalamin [12-14].

Allometric dose translation

An allometric dose translation was performed following FDA-recommended methodology for interspecies scaling [15]. The effective murine treatment-day dose, 1.0 μg per mouse administered subcutaneously on 5 consecutive days every month from the age of 3 months until natural death [8], was converted to a per-treatment-day Human Equivalent Dose (HED) using the body surface area normalization factor (Km mouse = 3; Km human = 37), yielding a projected human range of approximately 190 to 230 μg per treatment day for a 70-kg individual (see Table 1 for the complete calculation). Together, these three approaches provide the analytical framework on which the comparative and translational evaluations in the following sections are based.

The historical translation error: Epithalamin versus Epitalon

The origins of the dosing confusion can be traced to the developmental history of pineal peptide bioregulators in the former Soviet Union. Epithalamin was the first preparation to undergo extensive preclinical and clinical evaluation. It consists of a complex mixture of polypeptides extracted from bovine pineal glands, with molecular weights below 10 kDa, and was approved for medical use in the USSR in 1990 as a regulator of the neuroendocrine system [9]. Its clinical dosing was established empirically at 5 to 10 mg per day, administered intramuscularly for 5 to 10 consecutive days.

Epitalon was subsequently synthesized based on amino acid analysis of the Epithalamin extract, with the goal of identifying a defined molecular entity that could replace the crude preparation [2]. The tetrapeptide Ala-Glu-Asp-Gly was selected as the candidate active ingredient and was shown to replicate many of the biological effects observed with Epithalamin, including melatonin stimulation, telomerase activation, and lifespan extension [3, 7].

The critical translational problem arose from the fact that the clinical dosing conventions established for Epithalamin were carried forward to Epitalon without pharmacokinetic or pharmacodynamic adjustment. This conflation is pervasive in the literature. The landmark human study by Khavinson and Morozov [9], which followed 266 elderly persons over 6 to 8 years (with peptide treatment administered during the first 2 to 3 years), reported a 1.6- to 1.8-fold reduction in mortality in the Epithalamin-only group, a 2.5-fold reduction in patients receiving Thymalin plus Epithalamin, and a 4.1-fold reduction in those receiving the Thymalin plus Epithalamin combination annually for 6 years. Importantly, this study employed Epithalamin at 10 mg per day, not Epitalon. Similarly, the clinical improvements documented by Korkushko and colleagues at the Institute of Gerontology in Kiev, including normalized immune function, improved bone density, and restored carbohydrate metabolism, were achieved with Epithalamin at 5 to 10 mg per course day [16].

The Alzheimer's Drug Discovery Foundation (ADDF), in their 2017 Cognitive Vitality assessment, explicitly noted that the available human evidence pertains to Epithalamin, the crude extract, while the pharmacological literature on the synthetic peptide Epitalon is almost entirely limited

Table 1. Allometric dose translation from mouse to human (FDA method).

Parameter	Value
Effective murine dose [8]	1.0 μg/mouse, 5 consecutive days/month
Estimated mouse body weight	25–30 g
Weight-based murine dose	33–40 μg/kg
Km mouse / Km human	3/37 = 0.081
HED (μg/kg)	33–40 × 0.081 = 2.7–3.3 μg/kg
HED per treatment day for 70-kg human (μg)	189–231 μg per treatment day (≈ 190–230 μg)
Proposed therapeutic range (per treatment day; schedule to be defined)	100–300 μg per treatment day; treatment frequency and schedule to be defined

to animal and *in vitro* models [17]. This distinction has been largely overlooked by the translational community, resulting in a dosing paradigm that applies extract-derived milligram doses to a purified peptide that operates at a fundamentally different potency level.

Comparative potency and preclinical evidence

The most direct evidence for the potency differential between Epithalamin and Epitalon comes from a primate study conducted by Goncharova and colleagues at the Institute of Medical Primatology of the Russian Academy of Medical Sciences [10]. In this experiment, 18 young (6 to 8 years) and 20 old (20 to 27 years) female rhesus macaques were used to evaluate the circadian rhythm of melatonin secretion and its responsiveness to pineal peptide intervention. Old animals exhibited a nearly two-fold reduction in mean diurnal melatonin concentration, driven primarily by suppressed nocturnal secretion between 21:00 and 03:00.

Two treatment protocols were evaluated in separate but methodologically parallel experiments. Old animals received Epitalon at 10 μg per animal per day intramuscularly for 7 to 10 consecutive days, or Epithalamin at 5 mg per animal per day by the same route for 10 consecutive days. Both treatments restored nocturnal melatonin levels in old animals to values statistically indistinguishable from those of young controls. In old animals on day 10 of Epitalon treatment, the 22:00 melatonin concentration rose from a baseline of 44.8 ± 8.0 pg/mL to 80.7 ± 9.0 pg/mL ($p < 0.05$), compared to 87.6 ± 6.9 pg/mL in young untreated controls. Epithalamin produced a comparable normalization at the 21:00 time point, with values reaching 77 ± 9 pg/mL in old animals on day 10 *vs*. 73 ± 10 pg/mL in young controls. A summary of potency comparisons across biological models is provided in Table 2.

The key observation is that Epithalamin required a dose of 5 mg (5,000 μg) per animal to achieve the same functional endpoint that Epitalon achieved at 10 μg per animal. This represents a model- and endpoint-specific potency differential of approximately 500-fold and should be interpreted as a between-compound comparison within a single primate paradigm rather than as a globally transferable equivalence. The implication for human dosing is indicative rather than definitive: if the established human Epithalamin dose is 5 to 10 mg per day, then the pharmacologically equivalent Epitalon dose would, by direct linear analogy, be approximately 10 to 20 μg per treatment day, a figure that is directionally consistent with the microgram-range hypothesis but numerically below the allometric projection presented below.

Complementary evidence from invertebrate models reinforces this potency differential. In a series of studies using *Drosophila melanogaster*, Khavinson and Myl'nikov [12, 13] demonstrated that Epitalon exerted superior antioxidant effects, reducing lipid peroxidation products and enhancing catalase activity, at concentrations approximately 1,000-fold lower than those required for comparable effects with Epithalamin. As synthesized in the 2025 review by Araj *et al*. [14], these data confirm that Epitalon possesses a markedly higher specific biological activity than its parent extract, consistent with its nature as the purified active principle rather than a dilute component of a crude mixture.

The murine lifespan data provide an additional anchor point for dose estimation. Anisimov *et al*. [8] administered Epitalon to female Swiss-derived SHR mice at a dose of 1.0 μg per mouse subcutaneously on 5 consecutive days every month, from the age of 3 months until natural death (approximately 30–40 μg/kg per treatment day). Notably, the authors of this study explicitly compared the potency of the synthetic peptide to that of the parent extract and concluded that the effective concentration of Epitalon was approximately 1,000- to 5,000-fold lower than that of Epithalamin, a substantially wider potency margin than the 500-fold differential derived from the primate experiment above [10]. In the SHR mouse cohort, treatment did not significantly alter food consumption, body weight, or mean lifespan, but extended the lifespan of the last surviving 10% of the population by 13.3% and reduced chromosomal aberrations in bone marrow cells by 17.1% ($p < 0.05$). The selective effect on maximum rather than mean lifespan, alongside the reduction in genomic instability, is consistent with a targeted geroprotective effect rather than a generalized metabolic intervention.

The allometric translation of this dose is presented in Table 1. A standard laboratory mouse weighs approximately 25 to 30 grams, yielding a weight-based dose of approximately 33 to 40 μg/kg per treatment day. The FDA-recommended interspecies scaling factor from mouse to human, based on body surface area normalization, divides

Table 2. Comparative potency of Epithalamin and Epitalon across biological models.

Biological model	Epithalamin dose	Epitalon dose	Functional endpoint	Potency ratio
Rhesus macaque (old females)	5 mg/animal/day	10 μg/animal/day	Nocturnal melatonin restoration	≈ 500-fold
D. melanogaster	Reference effective concentration (1,000× higher than Epitalon)	0.00001% (w/w)	Lipid peroxidation, catalase activity	≈ 1,000-fold
BT474 cells (*in vitro*)	N/A	Peak at 0.2 μg/mL	Telomere elongation	Inverted U-curve (BT474 only)

Note: Potency ratios are model- and endpoint-specific and should not be interpreted as globally transferable equivalences across tissues, species, or biological endpoints. The inverted-U profile listed in the third row was specifically observed in BT474 (a malignant breast cancer cell line) but not in 21NT, the second cancer line tested in the same study, which showed a monotonic dose-dependent increase. The normal human cell lines IBR.3 and HMEC were tested at only one concentration (1.0 μg/mL) in that study and therefore do not yield a concentration-response curve [11].

the murine dose (in mg/kg) by a factor of 12.3, which is the ratio of human Km (37) to mouse Km (3) [15]. This conversion yields a per-treatment-day Human Equivalent dose of approximately 190 to 230 µg for a 70-kg individual, supporting a provisional microgram-range starting point of approximately 100 to 300 µg per treatment day, with treatment frequency and cycle length to be defined empirically.

Two important biological caveats apply to this allometric extrapolation. First, laboratory mice naturally express high levels of telomerase across multiple somatic tissues and possess long telomeres throughout their relatively short lifespan, whereas most human somatic cells (with the exception of stem and germ cell lineages) repress telomerase and undergo progressive telomere shortening with age. The biological substrate on which Epitalon acts is therefore qualitatively different between species. The murine model may underestimate the magnitude of telomerase-related effects in humans, where the absolute biological lever is potentially larger; alternatively, achieving comparable functional outcomes in humans may require dosing levels that cannot be derived from rodent data alone. Second, body surface area normalization assumes that systemic exposure scales predictably across species, an assumption that is most robust for small-molecule drugs with well-characterized clearance and that has not been formally validated for AEDG or related linear tetrapeptides. These considerations warrant explicit incorporation into the interpretation of any cross-species dose translation and motivate the framing of the proposed range as a translational hypothesis rather than a settled recommendation.

Pharmacokinetic and bioavailability considerations

Translational dose modelling for Epitalon is constrained by the limited pharmacokinetic data available for this compound. Published information on the absorption, distribution, metabolism, and elimination of synthetic AEDG in humans is sparse, and no formal human pharmacokinetic study of the synthetic tetrapeptide has been identified in the literature reviewed here. As a small linear tetrapeptide composed entirely of unprotected proteinogenic amino acids, Epitalon is expected to undergo rapid enzymatic degradation by aminopeptidases and other exopeptidases, with a short systemic half-life consistent with that observed for related linear peptides administered subcutaneously. Oral bioavailability is presumed to be low due to gastrointestinal proteolysis, although intranasal and sublingual formulations have been described in clinical and community practice without published bioequivalence data. To date, no formal human pharmacokinetic study of Epitalon has reported plasma half-life, clearance, or volume of distribution; available information on stability and bioavailability is largely indirect and extrapolated from general peptide pharmacology.

The dosing schedules used in published animal protocols (typically 5 to 10 consecutive days, sometimes daily, sometimes 5 days per week, often with repeated annual courses) are consistent with a model in which cumulative tissue exposure and the temporal pattern of intermittent stimulation are pharmacologically more relevant than peak plasma concentration. This pharmacokinetic profile, combined with the apparent non-monotonic dose-response observed at the cellular level, suggests that route, frequency, and exposure duration may modulate the apparent effective dose to a degree that body surface area normalization alone cannot capture. The absence of published human dose-ranging or pharmacokinetic studies of synthetic Epitalon is a primary driver of the uncertainty surrounding any human dosing estimate, including the range

Table 3. Distinguishing direct evidence from translational inference.

Evidence tier	Source	Status
Epithalamin human data	Khavinson & Morozov [9]; Korkushko *et al.* [16]	Directly observed clinical outcomes; pertain to a crude pineal extract that is pharmacologically distinct from synthetic Epitalon.
Epitalon animal data	Goncharova *et al.* [10] (primates); Anisimov *et al.* [8] (mice); Khavinson *et al.* [7] and Khavinson & Myl'nikov [12, 13] (*Drosophila*)	Directly observed biological effects of synthetic AEDG in non-human models, including melatonin restoration, lifespan extension, and antioxidant defense.
Epitalon *in vitro* data	Khavinson *et al.* [3]; Al-dulaimi *et al.* [11]; Grigor'ev *et al.* [18]; Lin'kova *et al.* [19]	Directly observed cellular effects under defined conditions, including telomere length extension via telomerase upregulation in normal cells (IBR.3, HMEC) and via Alternative Lengthening of Telomeres (ALT) in cancer cells (21NT, BT474). The inverted-U concentration-response was observed only in BT474, not in 21NT; normal cells were tested at only one concentration in the source study.
Translational extrapolations	Allometric scaling from murine treatment-day data (≈ 190–230 µg per treatment day); cross-compound dose derived from primate Epithalamin/Epitalon analogy (≈ 10–20 µg per treatment day); provisional microgram-range starting point of 100–300 µg per treatment day	Inferential rather than directly demonstrated; the proposed human range is a hypothesis derived from indirect cross-species and cross-compound reasoning and awaits formal human dose-finding validation.

proposed in this review, and is itself a notable gap in the translational pharmacology of this compound.

Cellular dynamics and non-linear dose-response

A recurring assumption in peptide therapeutics is that higher doses produce proportionally greater effects. The available *in vitro* evidence for Epitalon offers a partial challenge to this assumption and suggests that, at least in some cellular contexts, a biphasic or inverted U-shaped dose-response may apply, although the strength of this evidence varies by cell type.

In 2025, Al-dulaimi and colleagues at Brunel University London published the first fully independent study of Epitalon's effects on telomere dynamics in human cells [11]. Using two breast cancer cell lines (21NT and BT474) and two normal cell lines (IBR.3 fibroblasts and HMEC mammary epithelial cells), the investigators reported that Epitalon increases telomere length across all four cell types tested, providing independent validation of the core claim advanced by the Khavinson group. Cancer cells were treated daily with concentrations of 0.1, 0.2, 0.5, and 1.0 μg/mL for 4 days, while normal cells were treated daily with 1.0 μg/mL for 3 weeks; thus, a concentration-response curve was generated only for the cancer cell lines.

A mechanistically important cell-type-specific dichotomy emerged from this study: in the normal cell lines IBR.3 and HMEC, telomere elongation was associated with a significant increase in hTERT mRNA expression and corresponding telomerase enzyme activity, the classical telomerase-mediated mechanism. In the cancer cell lines 21NT and BT474, by contrast, hTERT expression was elevated but telomerase enzyme activity was not significantly enhanced; instead, telomere extension in cancer cells was driven by activation of the Alternative Lengthening of Telomeres (ALT) pathway, a recombination-based mechanism largely confined to malignant tissue. This mechanistic distinction is consequential for translational reasoning, because dose-response patterns observed in cancer cells reflect ALT biology that is largely absent in healthy human somatic tissue. Within the cancer-cell experiments, the dose-response patterns themselves differed between the two lines tested. In 21NT cells, telomere length increased dose-dependently from 0.2 to 1.0 μg/mL (significant at 0.5 and 1.0 μg/mL), with no inverted-U pattern. In BT474 cells, by contrast, telomere length reached its maximum at 0.2 μg/mL and was attenuated at the higher concentrations of 0.5 and 1.0 μg/mL, producing the inverted-U-shaped pattern. At the lowest concentration tested (0.1 μg/mL), the authors reported a decrease in telomere length in 21NT and a lower elongation rate in BT474, suggesting a possible inhibitory effect of very low concentrations on cancer-cell telomere maintenance. The normal cell lines were tested at only one concentration (1.0 μg/mL); accordingly, no concentration-response curve is available for normal human cells from this study, and the existence or absence of an inverted-U profile in non-malignant human tissue cannot be determined from these data. Taken together, these findings represent the strongest available independent evidence that Epitalon acts at sub-microgram-per-milliliter concentrations in human cells, but they do not constitute a general demonstration of an inverted-U dose-response across human tissue: the inverted-U was observed in only one of two cancer cell lines and the normal-cell experiments were not designed to detect it. Any inference about diminishing returns at higher concentrations in healthy human tissue therefore remains hypothesis-generating rather than demonstrated.

Earlier observations from the Epitalon literature describe additional concentration-dependent phenomena that, while suggestive, should be interpreted with caution. Khavinson and colleagues reported that the mitogenic activity of Epitalon on murine thymocytes peaked at extraordinarily low concentrations [18], and pluripotent cells of *Xenopus laevis* reportedly underwent neural differentiation at certain ng/mL concentrations but not at others [19]. These reports describe non-classical concentration-effect patterns and are mentioned here for completeness; they remain controversial within conventional pharmacology and are not load-bearing for the central translational argument advanced in this paper.

Taken together, the cellular and animal observations are most parsimoniously interpreted as a coherent suggestion that pharmacological efficacy is not obtained by escalating dose into the milligram range, rather than as proof of a uniform inverted-U profile applicable to all human tissues. This interpretation supports the broader translational hypothesis advanced here while explicitly acknowledging that the cellular evidence is, in itself, insufficient to define an optimal human dose (Table 3).

Discussion

The evidence assembled in this paper converges from multiple independent lines of investigation (primate pharmacology, invertebrate antioxidant assays, murine lifespan studies, allometric scaling, and *in vitro* dose-response characterization) on a consistent translational hypothesis: that the appropriate human dose range for Epitalon may lie in the low microgram range, with current indirect evidence pointing tentatively to approximately 100 to 300 μg per treatment day as a starting point for formal dose-finding studies (with treatment schedule and frequency to be defined), rather than the 5 to 10 mg per day currently employed by convention. If this hypothesis is correct, the current convention may represent roughly one to two orders of magnitude higher exposure than the range suggested by the present translational analysis.

The source of this error is historically understandable but pharmacologically unjustifiable. Epithalamin and Epitalon share functional endpoints such as melatonin restoration, telomerase activation, and antioxidant defense, yet differ by orders of magnitude in specific activity. The conflation of these two preparations in the transition from clinical

to community practice resulted in a dosing paradigm that treats a purified synthetic peptide as though it were a crude extract. This is analogous to dosing recombinant erythropoietin as though it were a crude kidney homogenate, or administering synthetic insulin at doses appropriate for a pancreatic extract. Such errors would be immediately recognized in conventional pharmacology but have persisted uncorrected in the peptide bioregulator field for over two decades.

The available safety information for Epitalon and Epithalamin should also be considered. Existing data, predominantly derived from animal studies and from uncontrolled clinical use of Epithalamin and related pineal preparations, do not currently indicate dose-limiting toxicity in the milligram range, and milligram-range exposure to synthetic Epitalon in the longevity community has not been associated with reports of serious adverse outcomes in the published literature. In the long-term murine experiment of Anisimov *et al*. [8] (1.0 μg per mouse on 5 consecutive days every month from 3 months of age until natural death), the authors reported no significant differences from controls in food consumption, body weight, or mean lifespan, alongside the documented geroprotective effects on maximum lifespan, chromosomal stability, and reduced leukemia incidence, and they explicitly characterized these findings as suggesting the safety of long-term administration of Epitalon in mice. This characterization pertains to the parameters monitored in that study and does not substitute for a formal toxicology evaluation in humans. However, the absence of formal toxicology and pharmacovigilance studies of synthetic Epitalon in humans means that no firm conclusion regarding the safety margin between effective and toxic doses can be drawn. The current absence of reported toxicity should not be confused with established safety, particularly given the heterogeneity of unregulated supply, in which peptide identity, purity, endotoxin burden, and contamination profile are not consistently verified.

Two distinct clinical uncertainties merit explicit acknowledgment. The first concerns the risk of overdosing under the current convention: if the inverted U-shaped concentration-response observed in malignant cells reflects a wider biological pattern, milligram-range systemic exposure may yield no incremental benefit and could plausibly produce paradoxical effects in selected tissues. The second concerns the risk of premature enthusiasm for very low-dose regimens before formal human dose-finding studies are conducted: a transition from milligram to microgram dosing on the basis of indirect, cross-species, and cross-compound evidence, while pharmacologically defensible, is not the same as a clinically demonstrated optimum. Both risks point to the same operational requirement, which is structured human dose-ranging research with quantitative biological and clinical endpoints.

Several limitations of the present analysis warrant acknowledgment. First, the comparative potency data derive from a limited number of studies, and the primate experiments by Goncharova *et al*. [10] were conducted in separate but parallel experimental groups rather than in a single head-to-head trial, which limits the precision of the potency ratio. Second, allometric scaling provides an estimate, not a definitive dose, and factors such as route-specific bioavailability, peptide half-life, and tissue distribution are not accounted for in the surface area normalization method. Third, the *in vitro* dose-response data from Al-dulaimi *et al*. [11] most informative for the present analysis were generated in a single malignant cell line (BT474); the second cancer line tested in the same study (21NT) showed a monotonic dose-dependent response without the inverted-U pattern, and the normal cell lines (IBR.3, HMEC) were tested at only one concentration, so the existence or absence of an inverted-U profile in non-malignant human tissue cannot be determined from these data; transferability of any single concentration-response relationship from cell culture to systemic *in vivo* dosing is therefore inherently uncertain. Fourth, no formal human dose-finding study of Epitalon exists in the published literature, and the proposed microgram range remains, at present, a hypothesis derived from indirect evidence.

Fifth, the literature search and synthesis were designed as a structured narrative review rather than a formal systematic review. Accordingly, screening was performed by a single reviewer, and formal study-level risk-of-bias assessment tools were not applied. The corpus was assembled according to prespecified eligibility criteria to address a defined translational dosing question and to trace the historical development of current dosing conventions. This approach may not capture every publication tangentially related to Epitalon or Epithalamin, but it prioritizes studies with identifiable compounds, relevant biological endpoints, and interpretable dose information. The conservative exclusion of ambiguous records was intended to improve the specificity of the comparative potency analysis.

Sixth, important species-specific biological differences exist between rodents and humans in telomerase expression and telomere length regulation, as discussed above, and these differences may modulate the magnitude and direction of any cross-species translation. Seventh, the published pharmacokinetic data on synthetic Epitalon are sparse, and any human dose estimate derived without route-specific exposure modelling necessarily inherits this uncertainty.

These limitations notwithstanding, the consistency of the evidence across species, endpoints, and methodologies provides a coherent and reproducible signal in a single direction. The 500-fold potency differential in primates, the 1,000-fold differential in *Drosophila*, the microgram-range efficacy in murine lifespan extension, the sub-microgram peak in cellular telomere elongation, and the allometric projection all converge on the same translational implication. The present synthesis identifies no published data point that, when scrutinized for compound identity and translational logic, supports the proposition that Epitalon requires milligram-range doses to achieve its characteristic biological effects.

Conclusions

The standard dosing of Epitalon at 5 to 10 mg per day appears to reflect a translational artifact, rooted in the uncritical adoption of dosing conventions established for a crude pineal extract (Epithalamin) and applied without adjustment to a purified synthetic peptide with dramatically higher specific activity. The preclinical evidence, when examined systematically, supports the hypothesis that the appropriate human dose range warrants formal investigation in the microgram range, with current indirect evidence pointing tentatively to approximately 100 to 300 µg per treatment day as a starting point for dose-finding studies, with treatment schedule and frequency to be defined.

We propose a paradigm shift in how Epitalon dosing is approached, both in research and in clinical application. Specifically, we recommend: (1) that future clinical investigations of Epitalon employ dose-finding designs beginning in the microgram range; (2) that published protocols and community guidelines explicitly distinguish between Epithalamin and Epitalon dosing; and (3) that the apparent non-linear dose-response characteristics of this peptide be incorporated into therapeutic reasoning, recognizing that escalation into the milligram range may not be necessary for biological effect and, in some cellular contexts, may not be advantageous.

The broader lesson extends beyond Epitalon to the entire field of peptide bioregulators, where translational dosing has historically proceeded by convention and analogy rather than by systematic pharmacological derivation. As these compounds attract increasing attention from both the research community and the public, the establishment of rational, evidence-based dosing frameworks becomes not merely desirable but essential.

This paper is offered as a hypothesis-generating translational analysis, intended to prompt formal human dose-finding research rather than to substitute for it.

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