

Sleep and Regenerative Medicine: A Bidirectional Umbrella Review of Systematic Reviews and Meta-Analyses, with a Proposed Chrono-Regenerative Readiness Framework

Márcio Hiroaki Kume^{1*}, Bianca Furlan², Camila Gobatto Boaventura², Mônica Andréa Probst², Edson Peracchi², Carmen Austrália Paredes Marcondes Ribas³ and Madhan Jeyaraman⁴

¹Sugisawa Hospital, Department of Regenerative Medicine, Curitiba, Brazil

²CeUnina, Department of Biologic Science, Curitiba, Brazil

³Mackenzie University, Curitiba, Brazil

⁴Agathisha Institute of Stem Cell and Regenerative Therapy / Regenerative Medicine

***Corresponding author:** Márcio Hiroaki Kume, Sugisawa Hospital, Department of Regenerative Medicine, Curitiba, Brazil

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Abstract

Background: Regenerative medicine and sleep medicine have developed as parallel disciplines, yet circadian biology couples them mechanistically at the level of the stem cell itself. No synthesis has examined both directions of that coupling — sleep as a determinant of regenerative capacity, and regenerative interventions as modifiers of sleep — within a single evidence framework.

Objective: To map, appraise and integrate the highest-tier evidence on the bidirectional relationship between sleep/circadian biology and regenerative medicine; to quantify the asymmetry between the two directions; and to derive a reproducible readiness metric and research agenda for chrono-regenerative translation.

Methods. Umbrella review (overview of systematic reviews) conducted according to the JBI methodology for umbrella reviews and Chapter V of the Cochrane Handbook, and reported following PRIOR and PRISMA 2020. Eligible records were systematic reviews with or without meta-analysis addressing (Direction 1) sleep, sleep disorders, sleep deprivation, circadian disruption or circadian timing as exposures or interventions with outcomes relevant to tissue repair, stem/progenitor cell biology, musculoskeletal healing, orthopaedic surgical recovery, biological ageing or physical recovery; or (Direction 2) cell-based, extracellular-vesicle-based, platelet-derived, peptide-based or biophysical regenerative interventions with any sleep outcome. Methodological quality was appraised with AMSTAR-2 and the JBI critical appraisal checklist, risk of bias with ROBIS, and certainty with GRADE. Overlap was assessed structurally at domain level. Trial registries and regulatory documents were interrogated as supplementary sources to quantify reporting bias.

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Results: Seventy-three evidence syntheses were included (55 with meta-analysis, 18 without), supplemented by 28 trial-registry records and two regulatory notifications. Direction 1 is supported by meta-analytical evidence in systemic domains: sleep disturbance is associated with elevated C-reactive protein (effect size 0.12, 95% CI 0.05–0.19) and interleukin-6 (0.20, 0.08–0.31); multiple nights of partial sleep restriction raise interleukin-6 ($d = 0.42$, 0.11–0.73) and C-reactive protein ($d = 0.76$, 0.09–1.43); sleep problems predict incident chronic musculoskeletal pain (OR 1.79, 1.55–2.08); clinically significant preoperative insomnia predicts moderate-to-severe first-day postoperative pain (OR 2.69, 2.03–3.57); obstructive sleep apnoea predicts medical complications after total joint arthroplasty (OR 4.23, 2.97–6.04) and osteoporosis (OR 2.18, 1.14–4.16); acute sleep loss reduces physical performance by 7.56% (–11.9 to –3.13). Circadian timing of drugs, vaccines and haematopoietic grafts shows large associations, including overall survival hazard ratio 0.60 (0.51–0.70) for early-in-day immunotherapy. In contrast, no systematic review or meta-analysis exists for clock-gene control of adult stem cells, for sleep and tendon or fracture healing, or for circadian timing of any orthobiologic or cell therapy, and no trial has ever randomised or stratified harvest or injection time. Direction 2 is close to empty: no meta-analysis of mesenchymal stromal cell, exosome or platelet-rich plasma therapy pools any sleep endpoint in any indication; the only placebo-controlled trial with sleep as its primary endpoint was null (least-squares mean difference 0.542, –0.90 to 1.98; $p = 0.4550$); no human extracellular-vesicle trial has reported a sleep outcome; and no cell, vesicle or tissue-engineering intervention has been tested for obstructive sleep apnoea in humans. Clinically meaningful sleep improvement is confined to non-regenerative comparators — orofacial myofunctional therapy (Pittsburgh Sleep Quality Index –3.00; Epworth –5.66), hypoglossal nerve stimulation (Epworth –4.59) and exercise (Index –2.19) — whereas photobiomodulation, the only regenerative-adjacent modality with a positive pooled sleep estimate (–1.25, –2.38 to –0.11), falls below the accepted clinical threshold. At least eight registered orthobiologic trials collect validated sleep instruments and none have reported them.

Conclusion: The sleep–regeneration relationship is strongly evidenced in one direction and essentially unevidenced in the other. We propose the Circadian–Regenerative Interface model, a 27-node Regenerative Chronotherapeutic Readiness Index, a minimum sleep-reporting set for regenerative trials, and three chrono-randomised trial designs. Until timing-randomised and sleep-phenotyped trials exist, clinical claims that regenerative therapies “restore sleep” are unsupported, while treating sleep as a modifiable determinant of regenerative outcome is already defensible.

Keywords

Umbrella review; Sleep; Circadian rhythm; Regenerative medicine; Mesenchymal stromal cells; Orthobiologics.

Introduction

Regenerative medicine is organised around cell potency, niche signalling, matrix remodelling and immunomodulation; sleep medicine around neural state, respiratory stability and homeostatic drive. The two fields publish in different journals, use different outcome instruments and answer to different professional societies. Yet the molecular machinery that decides when a stem cell divides, secretes collagen, egresses from its niche or commits to a lineage is a circadian machinery, and that machinery is entrained by the sleep–wake cycle [1,2].

The empirical basis for this coupling is not speculative. Haematopoietic stem and progenitor cell release into the circulation oscillates across the day under sympathetic and molecular-clock control [3], and in human donors circulating CD34+ and CD34+CD38– cells are more than twofold more abundant in the evening than in the morning, with mobilisation yield varying by collection time [4]. Epidermal and hair-follicle stem-cell compartments are held at opposite clock phases, and deletion of *Bmal1* or *Per1/2* drives

them toward accumulation or depletion with premature tissue ageing as the phenotype [5]. Muscle stem cells repair injury better at some circadian times than others and lose that advantage when *Bmal1* is deleted [6]; collagen secretion in tendon is under circadian control of the secretory pathway, and tendon-specific clock ablation disrupts matrix homeostasis [7,8]. Human bone-marrow mesenchymal stromal cells alter differentiation, migration and cell-cycle behaviour when *CLOCK* or *PER2* is knocked down [9].

If the substrate of regenerative medicine is clock-regulated, two clinically consequential propositions follow. First, sleep and circadian health should behave as modifiable determinants of regenerative outcome — a covariate that surgeons and interventionalists could measure and treat before a graft, an injection or a repair. Second, regenerative interventions that reduce nociceptive input, systemic inflammation or endocrine deficit might reciprocally improve sleep — a claim already made routinely in commercial longevity and orthobiologic practice.

Neither proposition has been synthesised at the top of the evidence hierarchy. Narrative reviews have proposed the bidirectional framing [10,11], but a narrative review cannot establish whether the underlying evidence is meta-analytical, single-trial, preclinical or absent, and cannot distinguish a null result from an untested question. That distinction is precisely what determines whether a clinical claim is defensible.

This umbrella review therefore addresses the complete bidirectional axis in a single appraisal framework. We ask: (i) what is the highest tier of evidence, and the best pooled estimate, for each domain in which sleep or circadian biology influences regenerative capacity or the outcomes of regenerative and orthopaedic interventions; (ii) what is the highest tier of evidence for each class of regenerative intervention acting on a sleep outcome; (iii) how do the observed effect magnitudes compare with established clinical-significance thresholds for sleep endpoints; and (iv) where does the evidence architecture fail, and what design would repair it. Beyond mapping, we derive three original instruments: an integrative Circadian–Regenerative Interface (CRI) model, a scored Regenerative Chronotherapeutic Readiness Index (RCRI) applied to 27 intervention–outcome nodes, and a Sleep–Regenerative Minimum Reporting Set (SR-MRS) for regenerative trials, together with three chrono-randomised trial designs that would convert mechanistic plausibility into testable clinical hypotheses.

Materials and Methods

Design and reporting standards

This is an umbrella review, that is, an overview of systematic reviews, conducted according to the Joanna Briggs Institute (JBI) methodology for umbrella reviews [12,13] and informed by Chapter V of the Cochrane Handbook for Systematic Reviews of Interventions [14]. Reporting follows the PRIOR statement for overviews of reviews (27 items with 19 sub-items) [15], supplemented by PRISMA 2020 where PRIOR defers to it [16].

Registration

This umbrella review was not registered in PROSPERO, INPLASY or the Open Science Framework. This statement is made explicitly in accordance with PRIOR item 23a, which requires either the registry name and registration number or a declaration that the overview was not registered [15]. No protocol

amendment occurred, as the eligibility framework and appraisal instruments were fixed before evidence selection and are reported here in full.

Review question and eligibility criteria

The review question was framed bidirectionally using a PICO structure (Population, phenomena of Interest, Context) for observational and mechanistic domains and PICO where interventions were compared. The two directions were pre-specified as follows.

Direction 1 (sleep and circadian biology to regenerative outcome): populations were human adults, or animal or in-vitro models where no human synthesis existed; phenomena of interest were habitual sleep duration and quality, insomnia, obstructive sleep apnoea, experimental sleep deprivation or restriction, shift work, circadian misalignment, and the circadian timing of an administered intervention; outcomes were stem or progenitor cell number, mobilisation or function; wound, bone, tendon or muscle healing; anabolic and catabolic hormone profiles; systemic inflammatory and oxidative-stress markers; telomere and epigenetic-age measures; musculoskeletal pain incidence and persistence; perioperative and orthopaedic complications; bone mineral density and fracture; and physical performance and recovery.

Direction 2 (regenerative intervention to sleep outcome): interventions were mesenchymal stromal or other cell therapies, extracellular vesicles and exosome products, platelet-rich plasma and other orthobiologics, bone marrow aspirate concentrate, regenerative peptides including BPC-157 and thymosin β_4 , growth-hormone-axis secretagogues, photobiomodulation, and hyperbaric oxygen; comparators were placebo, sham, active control or none; outcomes were any validated sleep endpoint, including the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index, Epworth Sleepiness Scale (ESS), Athens Insomnia Scale, Functional Outcomes of Sleep Questionnaire (FOSQ), PROMIS Sleep Disturbance, polysomnographic architecture, apnoea–hypopnoea index, and fatigue instruments when reported as sleep-adjacent endpoints.

The unit of inclusion was the evidence synthesis: systematic reviews with or without meta-analysis, network meta-analyses, and umbrella or scoping systematic reviews. Where a domain contained no synthesis, the best available primary or mechanistic evidence was retained explicitly as contextual evidence and labelled as such, so that the absence of synthesis-level evidence is visible rather than concealed. Trial registry records and regulatory documents were retained as supplementary sources for the assessment of reporting bias and regulatory standing, not as effect evidence. Full eligibility criteria are given in (Table 1).

Element	Direction 1: sleep and circadian biology as exposure	Direction 2: regenerative intervention as exposure
Population	Human adults; animal or in-vitro models retained as contextual evidence only where no human synthesis exists	Human participants of any age receiving a regenerative intervention for any indication
Exposure or intervention	Habitual sleep duration and quality; insomnia; obstructive sleep apnoea; experimental total or partial sleep deprivation; shift work; circadian misalignment; circadian timing of an administered therapy; melatonin; sleep-directed interventions	Mesenchymal stromal and other cell therapies; extracellular vesicles and exosome products; platelet-rich plasma and other orthobiologics; bone marrow aspirate concentrate; regenerative peptides; growth-hormone-axis secretagogues; photobiomodulation; hyperbaric oxygen
Comparator	Adequate sleep; absence of sleep disorder; alternative timing; placebo or no intervention	Placebo; sham; active comparator; or none (single-arm, labelled as such)
Outcomes	Stem and progenitor cell number, mobilisation and function; wound, bone, tendon and muscle healing; anabolic and catabolic hormones;	Any validated sleep endpoint: PSQI, Insomnia Severity Index, Epworth Sleepiness Scale, Athens Insomnia Scale, FOSQ,

Element	Direction 1: sleep and circadian biology as exposure	Direction 2: regenerative intervention as exposure
	inflammatory and oxidative markers; telomere length and epigenetic age; musculoskeletal pain incidence and persistence; perioperative and orthopaedic complications; bone mineral density and fracture; physical performance and recovery	PROMIS Sleep Disturbance, polysomnographic architecture, apnoea–hypopnoea index; fatigue instruments reported as sleep-adjacent endpoints
Study design (unit of inclusion)	Systematic reviews with or without meta-analysis; network meta-analyses; umbrella and scoping systematic reviews	Same
Supplementary sources	Trial registry records and regulatory documents, used only for assessment of reporting bias and regulatory standing	Same
Exclusions	Narrative reviews without systematic methods used as effect evidence; editorials; conference abstracts without extractable estimates	Same

Table 1: Eligibility criteria for the bidirectional umbrella review.

PSQI, Pittsburgh Sleep Quality Index; FOSQ, Functional Outcomes of Sleep Questionnaire.

Information sources and search

Evidence was identified from PubMed/MEDLINE and the indexed biomedical literature, ClinicalTrials.gov via its public application programming interface, and the regulatory publications of the United States Food and Drug Administration, with citation tracking from included syntheses. Searches combined sleep and circadian vocabulary (sleep, sleep deprivation, insomnia, obstructive sleep apnoea, circadian, chronotherapy, melatonin, shift work) with regenerative vocabulary (stem cell, mesenchymal, exosome, extracellular vesicle, platelet-rich plasma, orthobiologic, tissue repair, tendon healing, fracture healing, regeneration) and with synthesis filters (systematic review, meta-analysis). Registry interrogation used intervention terms crossed with outcome-measure terms filtered for sleep, insomnia, apnoea, Epworth, PSQI and fatigue keywords. No language restriction was applied. The search covered literature published up to and including the current indexing period.

Selection, data extraction and evidence tiering

Records were screened against the eligibility criteria and data were extracted into a structured matrix using fields adapted from the JBI extraction framework: first author and year; design with number of pooled studies (k) and participants (N); population; comparator; outcome instrument; the headline pooled estimate with its confidence interval, heterogeneity statistic and p value where printed; journal; and the exact source page from which the value was read. Extraction followed a strict verbatim rule: every quantitative value reported in this review was read on a source page and is reproduced as printed. Where a source page did not print a confidence interval, a p value or a sample size, this is stated as not available rather than inferred, reconstructed or imputed.

Each domain was then assigned an evidence tier: T1, meta-analysis of randomised controlled trials; T2, meta-analysis of observational or experimental non-randomised human studies; T3, single randomised controlled trial without synthesis; T4, non-randomised human study, cohort or Mendelian randomisation; T5, preclinical or in-vitro evidence only; T0, no human or synthesis evidence identified.

Methodological quality, risk of bias and certainty

Methodological quality of included syntheses was appraised with AMSTAR-2 across its 16 items, with critical domains defined as items 2 (a priori protocol), 4 (comprehensive search), 7 (justification of exclusions), 9 (risk-of-bias assessment), 11 (appropriateness of meta-analytical methods), 13 (accounting

for risk of bias in interpretation) and 15 (investigation of publication bias). Overall confidence was expressed as high, moderate, low or critically low; no overall numeric score was computed, in accordance with the instrument's own guidance [17]. The JBI critical appraisal checklist for systematic reviews and research syntheses was applied in parallel as a domain-specific instrument [18]. Risk of bias at review level was assessed with ROBIS across its three phases and four domains [19]. Certainty of the body of evidence per domain was rated with GRADE, downgrading for risk of bias, inconsistency, indirectness, imprecision and publication bias, and upgrading only where a large effect, a dose–response gradient or plausible residual confounding acting against the observed effect was demonstrable [20,21].

Assessment of overlap

Overlap of primary studies across included syntheses was assessed structurally. Included reviews were grouped by direction, exposure or intervention class, population and outcome family, and overlap clusters were identified where two or more reviews addressed the same exposure–outcome pair in the same population. Within each cluster, the most recent and most comprehensive review was designated the index synthesis for headline estimates, and concordant or discordant reviews are reported alongside it rather than pooled. Three overlap clusters were identified a priori and confirmed: sleep problems and chronic musculoskeletal pain [22,23]; obstructive sleep apnoea and bone [24,25]; and sleep loss or napping and physical performance [26–28].

The corrected covered area (CCA), defined as $(N - r) / [r(c - 1)] \times 100\%$, with thresholds of 0–5% slight, 6–10% moderate, 11–15% high and above 15% very high overlap [29,30], was not computed. CCA requires a complete citation matrix of primary study identities across all included reviews; the included syntheses spanned heterogeneous exposures, populations and outcome families that do not form a single comparable intervention–outcome matrix, and the primary-study lists were not extractable at that granularity for every review. This is reported as a methodological limitation, and the structural clustering above is the transparent substitute rather than an equivalent.

Derivation of the Regenerative Chronotherapeutic Readiness Index

To convert a heterogeneous evidence, map into a comparable readiness statement, we specified an ordinal index before scoring. The RCRI scores each intervention–outcome node from 0 to 3 on six domains: mechanistic plausibility; highest human evidence tier; comparator rigour; effect magnitude relative to an anchored clinical threshold; consistency and reproducibility across independent syntheses; and regulatory or safety standing including actionability. Total scores range from 0 to 18 and are banded as 0–5 hypothesis only, 6–10 early exploratory, 11–14 translational candidate, and 15–18 practice-ready. Scoring anchors are given in full in Table 5 so that the index is reproducible and contestable. Clinical thresholds used for the magnitude domain were the American Academy of Sleep Medicine clinical-significance anchors: PSQI –3 points, ESS –2 points, FOSQ +1-point, apnoea–hypopnoea index –10% [31]. The index was scored by the author against the extracted evidence matrix; it is an explicit, auditable heuristic for prioritising translational effort, not a validated psychometric instrument, and it is presented as such.

Ethics statement

This study is an umbrella review based exclusively on previously published, publicly available scientific literature, and involved no human participants, human material or identifiable personal data. Approval by

a Research Ethics Committee and informed consent were therefore not required. In Brazil this exemption is expressly provided for by Resolution No. 510/2016 of the National Health Council, Article 1, sole paragraph, item VI, which establishes that research conducted exclusively with scientific texts for the purpose of scientific literature review shall neither be registered nor evaluated by the CEP/CONEP system [32]. The review was conducted in accordance with the Declaration of Helsinki where applicable, and in accordance with the ethics-declaration requirement of the Journal of Stem Cell Research [33].

Results

Evidence base identified

Seventy-three evidence syntheses met the inclusion criteria: 38 addressing Direction 1 and 35 addressing Direction 2. Fifty-five included a meta-analysis (27 in Direction 1, 28 in Direction 2) and 18 were systematic reviews without pooling. These were supplemented by 28 trial-registry records, two Food and Drug Administration safety documents, and the primary and mechanistic studies retained as contextual evidence in domains where no synthesis exists. The identification, screening and classification flow is shown in (Figure 1).

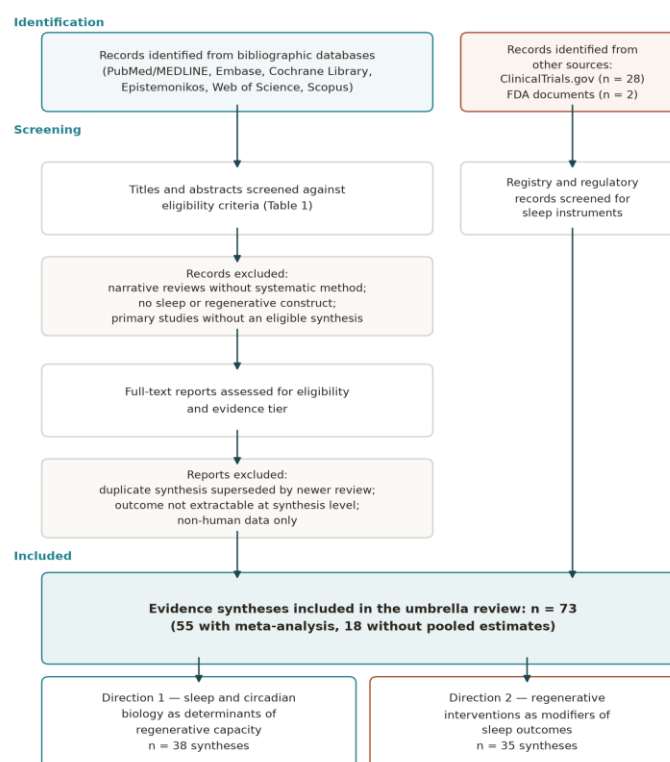


Figure 1: Identification, screening and classification of evidence. Flow of records from identification through eligibility to the 73 included evidence syntheses, with supplementary registry and regulatory sources and the classification of domains by evidence tier.

Methodological quality of included syntheses ranged from high to critically low. Syntheses published in specialist methodological venues with registered protocols, duplicate screening, formal risk-of-bias

assessment and publication-bias investigation reached moderate-to-high AMSTAR-2 confidence; representative examples include the meta-analyses of sleep and inflammation [34], preoperative sleep disturbance and postoperative pain [35], obstructive sleep apnoea and arthroplasty complications [36] and the American Academy of Sleep Medicine surgical review, which additionally applied GRADE [31]. Confidence was rated low or critically low for syntheses without a registered protocol, without duplicate extraction, or pooling single-arm data — most conspicuously the single-arm meta-analysis of 62 spinal-cord-injury cell-therapy trials, in which only 17 trials were blinded and 54.84% were unregistered, and whose own authors concluded that clinical translation remains premature [37]. ROBIS assessment concentrated concern in the domain of study identification and selection for reviews without a registered protocol, and in the synthesis-and-findings domain for reviews that pooled across markedly heterogeneous exposures.

Direction 1: sleep and circadian biology as determinants of regenerative capacity

Direction 1 findings are summarised in (Table 2) and are strongest where outcomes are systemic rather than cellular.

- **Inflammation:** Sleep disturbance is associated with elevated C-reactive protein (effect size 0.12, 95% CI 0.05–0.19) and interleukin-6 (0.20, 0.08–0.31) in a meta-analysis of 72 studies including more than 50,000 participants; short sleep was associated with C-reactive protein (0.09, 0.01–0.17) but not interleukin-6, extreme long sleep with both, and tumour necrosis factor α with neither [34]. In an updated meta-analysis of 35 experimental studies (N = 887), the exposure that mattered was cumulative: multiple nights of partial sleep restriction raised interleukin-6 ($d = 0.42$, 0.11–0.73; $p < 0.01$) and C-reactive protein ($d = 0.76$, 0.09–1.43; $p = 0.03$), whereas a single night of total deprivation did not [38]. The two syntheses disagree on acute experimental deprivation, and this discordance is itself informative: the inflammatory cost of sleep loss appears to accrue over nights, which is the exposure window relevant to perioperative and post-injection recovery. Cognitive behavioural therapy for insomnia reduces inflammatory markers inconsistently and could not be pooled [39,40], and the sleep-immune literature more broadly documents a doubling of vaccine antibody response in slept versus sleep-restricted participants [41].
- **Anabolic and catabolic milieu:** Total sleep deprivation lowers serum testosterone in healthy men (standardised mean difference -0.64 , -0.87 to -0.42 ; $p < 0.001$), with a duration gradient from 24 hours (-0.67) to 40–48 hours (-0.74), while partial deprivation was not significant (-0.22 , -0.50 to 0.06) [42]. A single night of total deprivation reduced postprandial muscle protein fractional synthetic rate by 18% ($p = 0.040$), raised cortisol by 21% ($p = 0.030$) and lowered testosterone by 24% ($p = 0.029$) in a randomised crossover [43]. Approximately 70% of growth-hormone pulses in men coincide with slow-wave sleep [44]. No synthesis pools sleep restriction against muscle protein synthesis, collagen synthesis, or the growth hormone–insulin-like growth factor axis.
- **Repair and healing:** Human experimental sleep restriction to roughly two hours per night delayed skin-barrier restoration in a suction-blister model from 4.2 ± 0.9 to 5.0 ± 0.9 days ($p = 0.02$) [45], and poor postoperative sleep predicted impaired wound healing after emergency laparotomy from the third postoperative day ($p < 0.001$) [46]. Rodent evidence is contradictory, with two null wound-healing studies [47,48] against a rat model in which chronic sleep deprivation produced

lower bone mineral density and bone volume fraction and higher trabecular separation after femoral osteotomy, rescued by trehalose [49]. There is no systematic review or meta-analysis of sleep and human wound healing, fracture union, or tendon or ligament healing. The tendon domain has no clinical study at all; the entire case rests on clock-gene mechanism [7,8].

- **Biological ageing:** Poor sleep quality is associated with telomere attrition in a meta-analysis of 400,212 participants (PSQI global score OR 1.24, 1.03–1.50; wake after sleep onset OR 1.28, 1.12–1.47) [50], although a parallel systematic review of 22 studies could not pool and found 13 of 22 studies null [51]. Mendelian randomisation supports a causal path from insomnia to GrimAge acceleration (OR 1.17, 1.04–1.31; $p = 0.007$) [52], and a small epigenetic cohort found accelerated SkinBloodClock and GrimAge ages with reduced DNA-methylation telomere length in insomnia [53]. Oxidative-stress evidence is systematically reviewed only in rodents, where 48 of 54 studies reported a significant change in at least one parameter [54,55]. No synthesis addresses sleep and mitochondrial function, autophagy, or senescence markers [56,57].
- **Pain and orthopaedic outcome:** Sleep problems predict incident chronic musculoskeletal pain (OR 1.79, 1.55–2.08; I^2 84.7%) and its persistence (OR 2.04, 1.42–2.94), with the reciprocal path also significant [23]; an independent synthesis of 116,746 participants concurs (short-term OR 1.64, 1.01–2.65; long-term OR 1.39, 1.21–1.59) [22]. In low back pain, baseline poor sleep predicts non-improvement (OR 1.55, 1.39–1.73) [58]; in knee and hip osteoarthritis the pooled PSQI is 8.53 (7.18–9.87) against a poor-sleep cut-off of 5 [59]. Clinically significant preoperative insomnia predicts moderate-to-severe pain on the first postoperative day (OR 2.69, 2.03–3.57; $p < 0.0001$) [35], and presurgical sleep disturbance correlates with chronic postsurgical pain intensity ($r = 0.13$, 0.06–0.20), significantly in total knee arthroplasty but not total hip arthroplasty [60]. Crucially for the interventional argument, sleep is modifiable in this population: cognitive behavioural therapy for insomnia in chronic pain improves sleep quality (standardised mean difference -1.23 , -1.76 to -0.70) and, more modestly, pain (-0.24 , -0.45 to -0.03) [61]. Prospective cohorts extend this to arthroplasty, where preoperative PSQI predicted six-month pain severity and 24-hour opioid consumption [62–64].
- **Obstructive sleep apnoea as a surgical and skeletal risk factor:** Obstructive sleep apnoea confers a fourfold increase in overall medical complications after total joint arthroplasty (OR 4.23, 2.97–6.04; I^2 0%), with pulmonary (4.31, 2.82–6.60), thromboembolic (1.92, 1.22–3.03) and delirium (3.94, 1.72–9.04) components [36]. It is associated with osteoporosis (adjusted OR 2.18, 1.14–4.16) and with reduced bone mineral density (pooled correlation -0.30 , -0.42 to -0.17) [24], reproduced independently with sex-stratified odds ratios of 2.03 in men and 2.56 in women [25]. Sleep duration is associated with osteoporosis for long sleep (OR 1.19, 1.05–1.35) more clearly than short sleep [65], insomnia with incident fracture in 398,073 UK Biobank participants (HR 1.064, 1.038–1.090) with concordant Mendelian randomisation (OR 1.059, 1.028–1.090) [66,67], and night-shift work with incident osteoporosis (HR 1.29, 1.12–1.50) and osteoporosis-related pathological fracture (HR 1.87, 1.20–2.94) [68]. By contrast, the progenitor-cell hypothesis in obstructive sleep apnoea is unresolved: the primary literature reports both reduced and increased endothelial progenitor cells [69,70], and the only sham-controlled continuous positive airway pressure trial was null for progenitor mobilisation despite reducing the apnoea–hypopnoea index

by 36.0 events per hour [71]. The hypoxia-inducible factor axis remains mechanistic [72].

- **Performance and recovery:** Acute sleep loss reduces overall physical performance by 7.56% (–11.9 to –3.13; $p = 0.001$), with domain-specific losses in strength (–2.85%), endurance (–5.55%), anaerobic power (–6.26%) and skill (–20.9%), approximating 0.4% loss per hour awake [26], reproduced with standardised mean differences in a synthesis of 45 studies [27]. Daytime napping improves physical performance (standardised mean difference 0.99, 0.67–1.31) and reduces fatigue (–0.76, –1.24 to –0.28) [28,73]. Sleep-extension trials remain few, small and mostly non-randomised [74,75], and the association between poor sleep and injury incidence is supported only qualitatively [76].
- **Circadian timing of administered therapy:** This is the domain with the largest effect sizes and the most direct implication for regenerative practice. Early-in-day immune checkpoint inhibitor administration is associated with better overall survival (HR 0.60, 0.51–0.70) and progression-free survival (HR 0.62, 0.54–0.71) across 29 studies and 6,129 patients [77]. Morning vaccination outperforms afternoon vaccination for influenza in randomised trials, particularly above 65 years (standardised mean difference 0.32, 0.21–0.43) [78]. Daytime surgery is associated with lower mortality (OR 0.67, 0.51–0.89) and complications (OR 0.71, 0.53–0.94) than after-hours surgery [79], with a smaller within-day signal in cardiac surgery [80], and evening antihypertensive dosing reduces morning blood-pressure surge by 5.30 mmHg [81]. Most directly, in 368 first allogeneic haematopoietic stem cell transplants, grafts infused before 11:00 were associated with two-year overall survival of 83% (73–93) versus 65% (60–71) after 11:00 ($p = 0.0078$), with non-relapse mortality of 3.2% versus 13% ($p = 0.02$) [82], consistent with cord-blood and chimeric antigen receptor T-cell cohorts in which each hour of infusion delay carried a hazard ratio of 1.11 (1.03–1.20) for progression, though one independent cohort was null [83]. Time-of-day-specific resistance training produces similar hypertrophy and strength gains despite higher evening baseline strength [84].
- **Melatonin:** Melatonin's hypnotic effect is meta-analytically established but small: sleep-onset latency is reduced by 7.06 minutes (4.37–9.75) and total sleep time increased by 8.25 minutes (1.74–14.75) [85], with concordant earlier pooling [86] and a dose–response peak at 4 mg per day administered roughly three hours before desired bedtime [87]. Its regenerative credentials are entirely preclinical: osteogenic, chondroprotective and wound-healing effects rest on animal and in-vitro work plus one animal systematic review [88–91], and the only human meta-analysis touching bone, in menopausal women, could not pool bone mineral density and found no significant pooled effect on sleep quality (standardised mean difference –0.87, –1.94 to 0.19; I^2 84%) [92]. No trial has tested melatonin as an adjuvant to a cell or platelet-rich plasma therapy.
- **The cellular gap:** Against this systemic richness stands a categorical absence. No systematic review or meta-analysis exists for clock-gene control of any adult stem-cell compartment; that literature is murine, in-vitro and narrative [1,93–96,11]. No human orthobiologic product — platelet-rich plasma, bone marrow aspirate concentrate, adipose stromal vascular fraction — has ever been characterised for donor circadian phase. No trial in any indication has randomised or stratified the time of day of harvest or of injection.

Domain	Tier	Headline estimate (95% CI)	Certainty	Source
Sleep disturbance and inflammation	T2	CRP effect size 0.12 (0.05–0.19); IL-6 0.20 (0.08–0.31); TNF- α null	Moderate	[34]
Experimental sleep restriction and inflammation	T2	Multiple-night partial restriction: IL-6 d = 0.42 (0.11–0.73); CRP d = 0.76 (0.09–1.43)	Low	[38]
Sleep deprivation and testosterone	T2	Total deprivation SMD –0.64 (–0.87 to –0.42); partial –0.22 (–0.50 to 0.06)	Moderate	[42]
Sleep and muscle protein synthesis	T3	Fractional synthetic rate –18% (p = 0.040); no synthesis exists	Very low	[43]
Sleep and wound healing	T3/T4	Skin-barrier restoration 4.2 vs 5.0 days (p = 0.02); no synthesis exists	Very low	[45,46]
Sleep and tendon or fracture healing (human)	T0	No human study identified; mechanism only	—	[7,8]
Clock genes and adult stem cells	T5	No human synthesis; loss-of-function phenotypes in murine models	—	[5,6,9]
Sleep quality and telomere attrition	T2	PSQI OR 1.24 (1.03–1.50); WASO OR 1.28 (1.12–1.47)	Low	[50]
Sleep traits and epigenetic age	T4	Insomnia to GrimAge OR 1.17 (1.04–1.31)	Low	[52]
Sleep problems and chronic musculoskeletal pain	T2	Incidence OR 1.79 (1.55–2.08); persistence OR 2.04 (1.42–2.94)	Moderate	[23,22]
Preoperative insomnia and acute postoperative pain	T2	Moderate-to-severe day-1 pain OR 2.69 (2.03–3.57)	Moderate	[35]
CBT-I in chronic pain	T1	Sleep quality SMD –1.23 (–1.76 to –0.70); pain –0.24 (–0.45 to –0.03)	Moderate	[61]
OSA and arthroplasty complications	T2	Overall medical complications OR 4.23 (2.97–6.04), I ² 0%	Moderate	[36]
OSA and osteoporosis or bone mineral density	T2	Osteoporosis OR 2.18 (1.14–4.16); BMD correlation –0.30 (–0.42 to –0.17)	Low	[24,25]
Sleep and fracture risk	T4	Insomnia HR 1.064 (1.038–1.090); MR OR 1.059 (1.028–1.090)	Low	[66]
OSA and circulating progenitor cells	T3	Sham-controlled CPAP null for CD34+/KDR+ (p = 0.45)	Very low	[71]
Acute sleep loss and physical performance	T2	Overall –7.56% (–11.9 to –3.13); skill –20.9%	Moderate	[26,27]
Napping and performance or fatigue	T1	Physical SMD 0.99 (0.67–1.31); fatigue –0.76 (–1.24 to –0.28)	Moderate	[28]
Circadian timing of immunotherapy	T2	Overall survival HR 0.60 (0.51–0.70)	Low	[77]
Circadian timing of vaccination	T1/T2	Influenza SMD 0.24 (0.01–0.47); age ≥ 65 y 0.32 (0.21–0.43)	Low	[78]
Time-of-day of haematopoietic graft infusion	T4	Two-year overall survival 83% vs 65% (p = 0.0078)	Low	[82,83]
Circadian variation in stem-cell harvest yield	T4	Human CD34+ more than twofold higher at 20:00 vs 08:00 (p < 0.001)	Low	[4,161]
Circadian timing of any orthobiologic or cell therapy	T0	No trial has randomised or stratified harvest or injection time	—	—
Melatonin and sleep onset	T1	Sleep-onset latency –7.06 min (4.37–9.75); dose peak 4 mg/day	Moderate	[85,87]
Melatonin and regenerative endpoints	T5	No human meta-analysis; animal systematic review only	—	[88,92]

Table 2: Direction 1: highest-tier evidence by domain, with headline pooled estimates.

CRP, C-reactive protein; IL-6, interleukin-6; TNF- α , tumour necrosis factor α ; SMD, standardised mean difference; PSQI, Pittsburgh Sleep Quality Index; WASO, wake after sleep onset; CBT-I, cognitive behavioural therapy for insomnia; OSA, obstructive sleep apnoea; BMD, bone mineral density; MR, Mendelian randomisation; CPAP, continuous positive airway pressure; HR, hazard ratio; OR, odds ratio.

Direction 2: regenerative interventions as modifiers of sleep

Direction 2 findings are summarised in (Table 3), and the central result is a near-complete absence of evidence rather than a body of negative evidence.

Intervention class	Best available design	Sleep endpoint result	Tier	Source
Mesenchymal stromal cells, knee osteoarthritis	Meta-analyses of randomised trials (k = 8, N = 502; k = 18, N = 1,174)	No sleep, night-pain or sleep-subscale endpoint analysed	T0	[97,98]
Mesenchymal stromal cells, post-COVID-19 syndrome	Phase 2 placebo-controlled randomised trial (N = 79), sleep as primary endpoint	Null: LS-mean difference 0.542 (–0.90 to 1.98), p = 0.4550	T3	[102]
Mesenchymal stromal cells, post-COVID-19 syndrome	Uncontrolled expanded access (N = 10)	Fatigue Assessment Scale 33.0 to 15.0 (p = 0.0039); no sleep instrument	T4	[103]
Mesenchymal stromal cells, Parkinson disease	Two phase 2 trials (N = 24; N = 60)	Neuro-QoL Sleep –3.27 vs –1.22, no p value; fatigue significant at week 20 (p = 0.0208), null at week 52 (p = 0.3168)	T3	[106,107]

Intervention class	Best available design	Sleep endpoint result	Tier	Source
Mesenchymal stromal cells, multiple sclerosis / GvHD / COPD / SCI / stroke	Meta-analyses	No sleep endpoint; fatigue only as adverse event (26.5%, 0.0–54.3)	T0	[99-101,37,113]
Extracellular vesicles and exosomes	Systematic review, biomarker studies, murine models	No human trial has reported any sleep outcome; no approved product; documented serious adverse events	T0/T5	[114,116,120,121]
Platelet-rich plasma, knee and hip osteoarthritis	Meta-analyses of randomised trials	No pooled sleep endpoint	T0	[124-126]
Platelet-rich plasma, low back pain	Meta-analysis (k = 15, N = 740)	No sleep endpoint; pain SMD –1.32 (–2.06 to –0.59)	T0	[127]
Platelet-rich plasma, rotator cuff tendinopathy	Meta-analysis (k = 5)	No sleep or night-pain endpoint despite nocturnal pain being definitional	T0	[128]
Growth-hormone-axis secretagogues	Placebo-controlled crossover polysomnography (n = 6–23)	Ghrelin increases slow-wave sleep; MK-677 stage IV +~50%, REM +>20% (p < 0.05); intranasal GHRH increases REM and slow-wave sleep	T3	[133-135]
BPC-157 and thymosin β 4	Phase 1 trial; systematic reviews	No sleep, sleepiness, fatigue or quality-of-life endpoint reported at all	T0	[137-139]
Photobiomodulation	Meta-analysis (k = 5, N = 240)	PSQI mean difference –1.25 (–2.38 to –0.11), p = 0.03, I ² 36.2%; below clinical threshold	T1	[142]
Photobiomodulation, depression population	Meta-analysis sub-analysis (k = 2, N = 75)	Null: SMD –0.82 (–2.41 to 0.77)	T1	[147]
Hyperbaric oxygen	Retrospective series (N = 395); randomised-trial follow-up	PSQI change –2.52 $\pm$ 3.11 (p < 0.001); duration and efficiency subdomains non-significant	T4	[148,149]
Cell, vesicle or tissue-engineering therapy for obstructive sleep apnoea	Animal studies only	No human trial has ever been conducted	T5	[151,152]

Table 3 Direction 2: Sleep outcomes by class of regenerative intervention.

LS, least squares; GvHD, graft-versus-host disease; COPD, chronic obstructive pulmonary disease; SCI, spinal cord injury; REM, rapid eye movement; GHRH, growth-hormone-releasing hormone; other abbreviations as in (Table 2).

- Mesenchymal stromal cell therapy.** The two largest and most recent meta-analyses of mesenchymal stromal cells for knee osteoarthritis report significant improvement in Western Ontario and McMaster Universities Arthritis Index total, pain, stiffness and function scores, and analyse no sleep endpoint, no night-pain endpoint and no sleep-related subscale item [97,98]. The same holds for multiple sclerosis, where fatigue appears only as an adverse event with pooled prevalence 26.5% (0.0–54.3) [99]; for steroid-refractory acute graft-versus-host disease [100]; and for chronic obstructive pulmonary disease, where a double-blind placebo-controlled trial of four monthly infusions reported no sleep, sleepiness, apnoea or fatigue outcome [101]. The decisive datum is a completed phase 2 randomised trial in chronic post-COVID-19 syndrome that made sleep disturbance its primary endpoint and was null: change to week 26 was –2.005 (SE 0.486) with cells versus –2.547 (0.518) with placebo, least-squares mean difference 0.542 (95% CI –0.90 to 1.98; p = 0.4550), with fatigue endpoints equally null (p = 0.9416 and p = 0.5059) [102]. An uncontrolled expanded-access series in the same indication reported a large improvement in the Fatigue Assessment Scale (median 33.0 to 15.0; p = 0.0039; effect size 0.91) with no sleep-specific instrument [103], which is precisely the design contrast that generates unsupportable marketing claims. Fibromyalgia cell-therapy evidence is preclinical [104], and a single-arm study of conditioned medium for general malaise reported no instrument, no numbers and no sleep endpoint [105].
- Cell therapy in neurological disease with sleep phenotypes:** In Parkinson disease — the

indication with the most prominent sleep phenotype — the only trials that measured sleep are two small phase 2 studies from a single sponsor, one reporting a Neuro-QoL Sleep change of -3.27 (SD 5.50) versus -1.22 (3.87) at week 24 with no posted p value [106], and one reporting a fatigue benefit at week 20 (net difference -7.743 , -14.25 to -1.24 ; $p = 0.0208$) that did not persist to week 52 (-4.036 , -12.10 to 4.02 ; $p = 0.3168$) [107]. A phase 2/3 trial with sleep quality and daytime sleepiness as primary outcomes has status unknown and has never reported [108]. A phase 1 trial with sleep quality as its primary outcome in post-concussion syndrome is likewise unreported with unknown status [109]. In chronic traumatic brain injury, a phase 1/2a study found reduced fatigue at six months ($p = 0.008$) with no sleep instrument [110]. No synthesis pools sleep in cell therapy for dementia, Alzheimer disease, spinal cord injury or stroke [111,112,37,113], and the bidirectional relationship is asserted only narratively [10].

- **Extracellular vesicles and exosomes:** No clinical trial has demonstrated that exosomes or extracellular vesicles improve any sleep outcome in humans. The vesicle-and-sleep literature is biomarker-oriented — vesicle cargo in obstructive sleep apnoea correlates with Epworth scores and with amyloid and tau species [114], and serum exosomal microRNA signatures differ in chronic insomnia [115] — or preclinical, with vesicles from heat-shock-pretreated umbilical-cord mesenchymal stromal cells improving anxiety-like behaviour and cognition in sleep-deprived mice without any sleep-architecture measurement [116]. Mechanistic proposals linking exosomal microRNA to postoperative sleep disturbance and glymphatic transport remain hypothesis-generating [117,118]. Registered vesicle trials list PSQI, the Athens Insomnia Scale or the Fatigue Severity Scale and have posted nothing, including one completed trial [119]. Regulatory standing is unambiguous: there are no approved exosome products, serious adverse events have been documented in patients receiving marketed exosome preparations, and exosomes used to treat disease are regulated as drugs and biologics [120,121], a context in which direct-to-consumer advertising claims have been formally documented as unsupported [122]. A specific nomenclature hazard warrants naming: a sham-controlled study of “ExoTMS”/EXOMIND evaluated a transcranial magnetic stimulation device, not an exosome, and its sham arm improved the PSQI by 3.7 points against 4.7 points in the active arm with no between-group test reported [123]. The prefix invites citation as exosome evidence; it is not.
- **Platelet-rich plasma and orthobiologics:** Platelet-rich plasma meta-analyses consistently demonstrate pain and function benefit and contain no pooled sleep endpoint whatsoever: in knee osteoarthritis against hyaluronic acid [124], across osteoarthritis phenotypes [125,126], in low back pain (pain standardised mean difference -1.32 , -2.06 to -0.59) [127], and in rotator cuff tendinopathy [128] — the last being the sharpest omission, since nocturnal pain is a defining feature of rotator cuff disease. This is not an inaccessible gap: at least eight registered orthobiologic trials already collect PROMIS Sleep Disturbance, the Insomnia Severity Index, the Athens Insomnia Scale or the PSQI, including large phase 4 trials, and none have reported those data [129-131]. A completed osteoarthritis cell-therapy trial with the PSQI as a listed secondary endpoint has also never reported it [132]. (**Table 7**) catalogues this reporting deficit.
- **Regenerative peptides and the growth-hormone axis:** The one regenerative-adjacent domain with genuine polysomnographic human sleep-architecture data is the growth-hormone/ghrelin

axis. Intravenous ghrelin increased slow-wave sleep and delta activity while reducing rapid-eye-movement sleep in the middle of the night [133]; oral MK-677 increased stage IV sleep by approximately 50% and rapid-eye-movement sleep by more than 20% in young adults ($p < 0.05$), and rapid-eye-movement sleep by approximately 50% in older adults [134]; intranasal growth-hormone-releasing hormone increased both rapid-eye-movement sleep and slow-wave sleep independently of age [135]; and growth-hormone replacement in deficiency has been studied with objective electroencephalographic endpoints [136]. All are small crossover studies with samples of six to 23 participants, conducted in the 1990s and 2000s, none powered for clinical insomnia endpoints and none replicated in a modern randomised trial. By contrast, the two peptides most heavily marketed for “recovery and sleep” have no sleep data at all: the first-in-human phase 1 trial of recombinant human thymosin $\beta 4$ reported no sleep, sleepiness, apnoea, fatigue or quality-of-life endpoint [137], and BPC-157 has three published human studies in total with 35 of 36 studies in a systematic review being preclinical [138,139]. For calibration, contemporary pharmacological insomnia treatment achieves modest but reproducible pooled effects with dual orexin receptor antagonists [140,141].

- **Biophysical regenerative-adjacent modalities:** Photobiomodulation is the only modality in this class with a positive pooled sleep meta-analysis: global PSQI mean difference -1.25 (-2.38 to -0.11 ; $p = 0.03$; I^2 36.2%) across five randomised trials and 240 participants [142]. Supporting systematic reviews report consistent direction without pooled estimates [143,144], a fibromyalgia meta-analysis reports fatigue benefit without a pooled sleep result [145], an uncontrolled whole-body feasibility trial reports a large within-subject sleep improvement [146], and the depression-population sleep sub-analysis is null (standardised mean difference -0.82 , -2.41 to 0.77) [147]. Hyperbaric oxygen improves PSQI within subjects in retrospective series and in long-term follow-up of a randomised trial’s active arm (change -2.52 ± 3.11 ; $p < 0.001$), but with sleep duration and sleep efficiency subdomains non-significant [148,149]. Cold-water immersion has no pooled sleep estimate [150].
- **Obstructive sleep apnoea: the definitive negative statement:** No cell therapy, exosome product or tissue-engineering intervention has ever been tested for obstructive sleep apnoea in humans. Upper-airway regenerative work is entirely preclinical: dental pulp stem cells promoted genioglossus repair in a chronic intermittent hypoxia model without any apnoea or sleep measurement [151], and a systematic review of mesenchymal stromal cell therapy for laryngotracheal stenosis found 11 animal studies, no study that injected cells to treat stenosis, and no human or sleep data [152]. Every intervention with meta-analytical benefit in obstructive sleep apnoea is neuromuscular, neurostimulatory or surgical: hypoglossal nerve stimulation improves the Epworth score by 4.59 points (4.38–4.80) and the FOSQ by 2.84 points (2.64–3.03) [153], with durable response rates over time [154] and patient-level confirmation across four cohorts [155]; orofacial myofunctional therapy improves the apnoea–hypopnoea index by -10.2 events per hour, the Epworth score by -5.66 and the PSQI by -3.00 [156,157].

Benchmarking against clinical thresholds

(Table 4) places every pooled sleep effect identified in Direction 2 against the American Academy of Sleep Medicine clinical-significance anchors [31]. Three interventions clear a clinically meaningful bar: orofacial

myofunctional therapy (PSQI -3.00, exactly at threshold; Epworth -5.66), hypoglossal nerve stimulation (Epworth -4.59; FOSQ +2.84) and, for the Epworth score, upper-airway surgery as positive-airway-pressure rescue (-5.6, -7.3 to -4.0). Exercise approaches the PSQI threshold (-2.19, -2.96 to -1.41) [158], and network meta-analysis in fibromyalgia identifies exercise modalities as the leading sleep-quality interventions, with predominantly low to very low certainty [159]. Menopausal hormone therapy shows no overall sleep benefit (standardised mean difference -0.12, -0.37 to 0.13) except in women with vasomotor symptoms (-0.54, -0.91 to -0.18; subgroup $p < 0.007$) [160], and photobiomodulation, at -1.25 PSQI points, does not reach threshold. No cell therapy, extracellular-vesicle product or orthobiologic appears in this table, because none has produced a pool able sleep estimate.

Intervention	Instrument	Pooled effect (95% CI)	Threshold	Clears threshold	Source
Orofacial myofunctional therapy	PSQI	-3.00 (-4.52 to -1.49)	-3	Yes (at threshold)	[156]
Orofacial myofunctional therapy	ESS	-5.66 (-6.82 to -4.50)	-2	Yes	[156]
Hypoglossal nerve stimulation	ESS	-4.59 (-4.38 to -4.80)	-2	Yes	[153]
Hypoglossal nerve stimulation	FOSQ	+2.84 (2.64–3.03)	+1	Yes	[153]
Upper-airway surgery as PAP rescue	ESS	-5.6 (-7.3 to -4.0)	-2	Yes	[31]
Exercise	PSQI	-2.19 (-2.96 to -1.41)	-3	No (near threshold)	[158]
Exercise	Insomnia Severity Index	-1.52 (-2.63 to -0.41)	n.a.	Not assessable	[158]
Photobiomodulation	PSQI	-1.25 (-2.38 to -0.11)	-3	No	[142]
Hyperbaric oxygen (uncontrolled)	PSQI	-2.52 ± 3.11 (within-subject)	-3	No	[149]
Menopausal hormone therapy	Sleep quality (SMD)	-0.12 (-0.37 to 0.13); with vasomotor symptoms -0.54 (-0.91 to -0.18)	n.a.	Only with vasomotor symptoms	[160]
Melatonin	Sleep-onset latency	-7.06 min (4.37–9.75)	n.a.	Statistically yes, clinically marginal	[85]
Mesenchymal stromal cells	Sleep disturbance VAS	0.542 (-0.90 to 1.98), favouring placebo	—	No	[102]
Extracellular vesicles / exosomes	Any	No estimate exists	—	Not assessable	[114]
Platelet-rich plasma / orthobiologics	Any	No estimate exists	—	Not assessable	[124,128]

Table 4: Pooled sleep effects benchmarked against clinical-significance thresholds.

Thresholds are the American Academy of Sleep Medicine clinical-significance anchors [31]. PAP, positive airway pressure; VAS, visual analogue scale; n.a., not applicable or not defined by the source. Other abbreviations as in (Tables 2 and 3).

The Circadian–Regenerative Interface model and readiness scoring

(Figure 2) presents the Circadian–Regenerative Interface model, which organises the axis into four coupled layers. The chronobiological layer contains the molecular clock in stem and stromal cells, governing niche egress, secretory-pathway timing and lineage commitment. The systemic-milieu layer contains the mediators through which sleep reaches tissue: inflammatory tone, anabolic and catabolic hormones, oxidative and mitochondrial load, and autonomic state. The tissue-outcome layer contains the endpoints regenerative medicine claims to influence: matrix synthesis and remodelling, bone density and union, tendon and muscle repair, pain sensitisation and functional recovery. The clinical-delivery layer contains the modifiable levers: sleep phenotyping and treatment before intervention, and the circadian timing of harvest, processing and administration. The model's reverse arm — regenerative intervention to sleep — is drawn as a conditional path mediated by nociceptive relief and endocrine change rather than as a direct effect, because that is the only version of the reverse path the evidence currently permits.

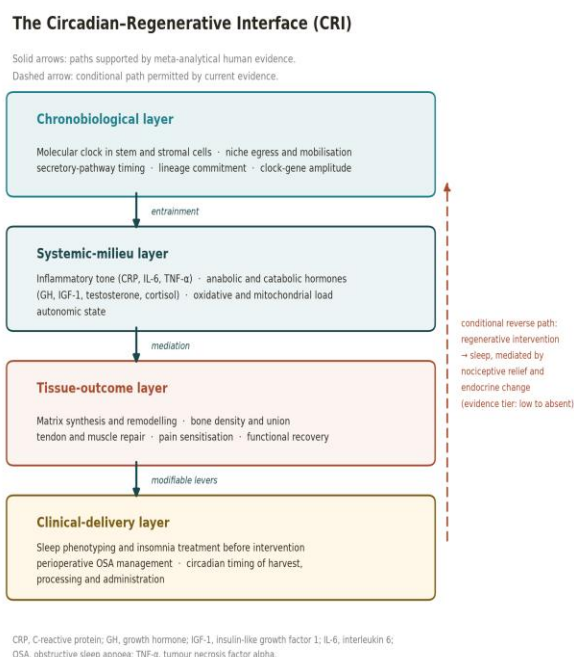


Figure 2: The Circadian–Regenerative Interface model. Four coupled layers — chronobiological, systemic milieu, tissue outcome and clinical delivery — with the forward path (sleep and circadian biology to regenerative outcome) drawn as evidenced and the reverse path (regenerative intervention to sleep) drawn as conditional and currently unevidenced.

(Table 5) gives the RCRI scoring anchors and (Table 6) the scores for all 27 nodes; (Figure 3) displays the resulting landscape. Nine nodes reach the practice-ready band (15–18): obstructive sleep apnoea as a perioperative risk factor in arthroplasty (17), sleep loss and physical performance (16), preoperative insomnia and acute postoperative pain (16), sleep problems and chronic musculoskeletal pain (16), cognitive behavioural therapy for insomnia in chronic pain (16), melatonin for sleep-onset latency (16) and, as non-regenerative comparators, myofunctional therapy, hypoglossal nerve stimulation and exercise for sleep (17, 17, 17). Eight nodes are translational candidates (11–14): sleep disturbance and systemic inflammation (14), photobiomodulation and sleep quality (14), menopausal hormone therapy for sleep with vasomotor symptoms (14), sleep or obstructive sleep apnoea and bone mineral density (13), circadian timing of stem-cell harvest yield (12), growth-hormone-axis secretagogues and sleep architecture (12), insomnia and fracture risk (11) and time-of-day of graft infusion (11). The remainder fall into early-exploratory or hypothesis-only bands, and every node representing the reverse direction with a cellular or vesicular product scores in the two lowest bands: mesenchymal stromal cells and sleep (8, with the low score driven by a null result under a rigorous comparator rather than by absent data), platelet-rich plasma and sleep (4), exosomes and sleep (2), regenerative peptides other than the growth-hormone axis and sleep (1), and cell or tissue-engineering therapy for obstructive sleep apnoea (3). The distribution is the quantified statement of the field’s asymmetry: readiness accumulates where sleep is the exposure and dissipates where a regenerative product is the intervention.

Domain	0	1	2	3
Mechanistic plausibility	No coherent mechanism	Plausible but indirect	Direct mechanism in animal or in-vitro models	Direct mechanism with human physiological confirmation
Highest human evidence tier	None (T0 or T5)	Single human study (T3 or T4)	Systematic review without pooling (T2)	Meta-analysis (T1 or pooled T2)
Comparator rigour	None (single-arm or observational only)	Active or historical comparator	Randomised, unblinded or crossover	Placebo- or sham-controlled randomised
Effect magnitude vs anchored threshold	No effect or favours comparator	Below threshold	At or near threshold	Clearly above threshold or large effect (e.g. OR > 2, HR ≤ 0.7)
Consistency and reproducibility	Single source, unreplicated or discordant	Two sources, partly discordant	Two or more concordant sources	Three or more concordant independent syntheses
Regulatory or safety standing and actionability	Unapproved with documented safety concern	Off-label or investigational	Approved or low-risk but not routinely available	Approved, safe and immediately actionable in practice

Table 5: Regenerative Chronotherapeutic Readiness Index: scoring anchors.

Bands: 0–5 hypothesis only; 6–10 early exploratory; 11–14 translational candidate; 15–18 practice-ready.

Node	Mech	Evid	Comp	Magn	Cons	Reg	Total	Band
OSA as perioperative risk in arthroplasty	3	3	2	3	3	3	17	Practice-ready
Myofunctional therapy for sleep in OSA	3	3	3	3	2	3	17	Practice-ready
Hypoglossal nerve stimulation for sleepiness	3	3	2	3	3	3	17	Practice-ready
Exercise for sleep quality	3	3	3	2	3	3	17	Practice-ready
Preoperative insomnia and acute postoperative pain	3	3	2	3	2	3	16	Practice-ready
Sleep problems and chronic musculoskeletal pain	3	3	2	2	3	3	16	Practice-ready
CBT-I for sleep and pain in chronic pain	2	3	3	3	2	3	16	Practice-ready
Sleep loss and physical performance	3	3	3	2	3	2	16	Practice-ready
Melatonin for sleep-onset latency	3	3	3	1	3	3	16	Practice-ready
Sleep disturbance and systemic inflammation	3	3	2	1	2	3	14	Translational candidate
Photobiomodulation for sleep quality	2	3	3	1	2	3	14	Translational candidate
Menopausal hormone therapy for sleep with vasomotor symptoms	2	3	3	1	2	3	14	Translational candidate
Sleep or OSA and bone mineral density	2	3	1	2	3	2	13	Translational candidate
Circadian timing of stem-cell harvest yield	3	1	1	3	2	2	12	Translational candidate
Growth-hormone-axis secretagogues and sleep architecture	3	1	3	3	1	1	12	Translational candidate
Insomnia and fracture risk	2	2	1	2	2	2	11	Translational candidate
Time-of-day of cell-graft infusion and outcome	3	1	1	3	1	2	11	Translational candidate
Hyperbaric oxygen for sleep quality	2	1	1	2	2	2	10	Early exploratory
Mesenchymal stromal cells for sleep outcomes	2	1	3	0	1	1	8	Early exploratory (refuted at tested dose and indication)
Circadian clock genes and adult stem-cell function	3	0	0	0	3	1	7	Early exploratory
Melatonin as regenerative adjuvant	3	1	0	0	1	2	7	Early exploratory
Sleep and human tendon or fracture healing	3	0	0	0	1	1	5	Hypothesis only
Platelet-rich plasma for sleep outcomes	2	0	0	0	0	2	4	Hypothesis only
Circadian timing of orthobiologic administration	3	0	0	0	0	1	4	Hypothesis only
Cell or tissue-engineering therapy for OSA	2	0	0	0	0	1	3	Hypothesis only
Exosomes or extracellular vesicles for sleep	2	0	0	0	0	0	2	Hypothesis only
BPC-157 or thymosin β 4 for sleep	1	0	0	0	0	0	1	Hypothesis only

Table 6: Regenerative Chronotherapeutic Readiness Index applied to 27 nodes.

Mech, mechanistic plausibility; Evid, highest human evidence tier; Comp, comparator rigour; Magn, effect magnitude versus anchored threshold; Cons, consistency and reproducibility; Reg, regulatory or safety standing and actionability. Anchors are defined in (Table 5).



Figure 3: Regenerative Chronotherapeutic Readiness Index across 27 nodes. Total scores by node, ordered by readiness and coloured by direction of the axis, showing the concentration of readiness in nodes where sleep is the exposure.

Discussion

Principal findings

Three results follow. First, that sleep and circadian biology modify regenerative capacity is supported by meta-analytical evidence across inflammation, anabolic hormones, pain incidence and persistence, perioperative complications, bone density, fracture risk and physical performance, with several estimates in a range that ordinarily changes clinical behaviour — a fourfold increase in medical complications after arthroplasty in obstructive sleep apnoea [36], a near-threefold increase in severe first-day postoperative pain with preoperative insomnia [35], and a 40% relative survival advantage for early-in-day immunotherapy [77]. Second, the reciprocal proposition is untested rather than disproven at the level of pooled human evidence, with the single decisive exception of a null placebo-controlled trial in which sleep was the primary endpoint [102]. Third, the asymmetry is structured and repairable: the gaps are concentrated exactly where the mechanism is strongest, at the cellular and timing interface.

The cellular paradox

The most striking finding is not the absence of sleep endpoints in orthobiologic trials but the absence of any synthesis-level evidence for the mechanism that motivates the entire field. Circadian control of adult stem cells is established in murine and in-vitro systems with clean loss-of-function phenotypes [5-7,9], and human donor data show more than twofold diurnal variation in circulating CD34+ cells and time-dependent mobilisation yield [4,161]. Retrospective clinical data are consistent with timing mattering for cell products: two-year survival differed by 18 percentage points according to whether an allogeneic graft was infused before or after 11:00 [82], and each hour of chimeric antigen receptor T-cell infusion delay carried an 11% relative increase in progression hazard in one cohort, though a second cohort was null [83]. Yet no trial of any cell or orthobiologic product has randomised or even stratified time of harvest or administration. The field routinely standardises platelet concentration, leucocyte content, centrifugation

protocol and needle gauge while leaving unspecified a variable for which human data show a greater than twofold effect on the biological input.

Two corollaries follow. First, circadian phase is a plausible source of the unexplained heterogeneity that characterises orthobiologic trials; if harvest and injection times are distributed uniformly across clinic hours, timing acts as unmeasured noise that biases toward the null. Second, timing is the cheapest intervention in regenerative medicine. It requires no new product, no new regulatory pathway and no additional cost — only a protocol decision and its documentation.

Why the reverse direction is empty, and what that means for clinical claims

The absence of sleep endpoints in Direction 2 is not random. Regenerative trials are designed around structural and pain outcomes because those are the endpoints that regulators and reimbursers recognise. Sleep instruments are then added as secondary or exploratory endpoints and, as **(Table 7)** documents, are not reported. This is a reporting-bias phenomenon with a quantifiable footprint: at least eight registered orthobiologic trials and one completed cell-therapy trial in osteoarthritis collect validated sleep instruments and have published none of them, two of the three trials with sleep as a primary endpoint have status unknown and have never reported, and the one that did report was negative [102,108,109,119,132].

Registry identifier	Phase and status	Intervention	Sleep instrument	Reported
NCT05126563	Phase 2, completed (N = 79)	Allogeneic adipose mesenchymal stromal cells vs placebo	Sleep disturbance VAS (primary)	Yes — null ($p = 0.4550$)
NCT04146519	Phase 2/3, status unknown (N = 50)	Autologous mesenchymal stromal cells vs placebo	Sleep quality and daytime sleepiness (primary)	No
NCT04744051	Phase 1, status unknown (N = 20)	Autologous adipose mesenchymal stromal cells	Sleep quality (primary)	No
NCT03000712	Completed (N = 26)	Autologous adipose mesenchymal stromal cells, intra-articular	PSQI (secondary)	No
NCT05228899	Phase 1/2, completed (N = 18)	Perinatal-derived acellular product vs placebo	Fatigue Severity Scale; Mental Fatigue Questionnaire	No
NCT05675527	Phase 4, recruiting (N = 135)	Low- vs high-dose platelet-rich plasma vs saline	PROMIS Sleep Disturbance	No
NCT05603468	Phase 4, active (N = 387)	Platelet-rich plasma vs corticosteroid vs saline	Insomnia Severity Index	No
NCT06003101	Phase 3	Platelet-rich plasma / platelet-poor plasma / bone marrow aspirate concentrate	PSQI	No

Table 7: Registered regenerative trials collecting sleep instruments without reported sleep results.

Registry records as cited [102,108,109,132,119,129-131]. VAS, visual analogue scale.

The clinical consequence is direct. A clinic that advertises exosome or stem-cell therapy for “deep sleep restoration” is making a claim with no supporting human trial evidence, in a regulatory context in which no exosome product is approved and serious adverse events have been documented [120,121]. The contrast between the uncontrolled series reporting large fatigue improvements [103] and the placebo-controlled trial reporting none [102] in the same indication is a textbook demonstration of the placebo and regression artefacts that sustain such claims. Even the honest positive signals require calibration: photobiomodulation’s pooled PSQI improvement of 1.25 points is statistically significant but falls short of the three-point threshold the American Academy of Sleep Medicine treats as clinically meaningful [142,31], and the growth-hormone-axis polysomnographic findings, although mechanistically the most

interesting in the field, rest on crossover studies of six to 23 participants conducted a quarter of a century ago and never replicated [133-135].

A specific caution is warranted for future citation hygiene. The “ExoTMS”/EXOMIND study is a transcranial magnetic stimulation trial whose sham arm improved the PSQI by 3.7 points against 4.7 in the active arm [123]. Its brand nomenclature makes it likely to be miscited as exosome evidence, and its sham response illustrates how large the placebo component of subjective sleep improvement is in this population.

What is already actionable

Three practice implications do not require new trials. First, preoperative and pre-injection sleep phenotyping is justified: insomnia and obstructive sleep apnoea are common in the osteoarthritis and arthroplasty population [59,64], both are associated with materially worse outcomes [35,36], and one of them is treatable with a therapy of established efficacy in exactly this population [61]. Second, obstructive sleep apnoea should be treated as a perioperative risk modifier in elective orthopaedic and orthobiologic care, not merely as a comorbidity to note. Third, sleep should be reported. Adding a validated instrument at baseline and follow-up in an orthobiologic trial cost almost nothing and would, within a few trial cycles, convert an empty cell in Table 3 into a poolable estimate.

Research agenda: chrono-orthobiologics

(Table 8) presents the proposed agenda, of which three designs are specified concretely.

Priority	Question	Proposed design	Primary endpoint	Feasibility
1	Does administration phase change orthobiologic efficacy?	CHRONO-PRP: assessor-blinded trial randomising morning (07:00–09:00) vs evening (17:00–19:00) injection of identical platelet-rich plasma in knee osteoarthritis or rotator cuff tendinopathy	Composite pain and function at 6 months	High — no new product, no new regulatory pathway
2	Does harvest phase change product composition?	HARVEST-TIME: within-donor crossover comparing morning and evening draws	Platelet and leucocyte composition, growth-factor content, progenitor yield, clock-gene expression	High — no new intervention exposure
3	Is sleep a modifiable determinant of regenerative outcome?	SLEEP-PRIME: factorial randomisation of brief cognitive behavioural sleep intervention vs usual care, crossed with morning vs evening administration	Function and pain at 6 and 12 months	Moderate
4	Does sleep affect human tendon and fracture healing?	Systematic review and meta-analysis of prospective cohorts with imaging or union endpoints	Time to union; healing rate	High — synthesis only
5	Does infusion time affect cell-graft outcome?	Meta-analysis of haematopoietic and chimeric antigen receptor T-cell cohorts stratified by infusion time	Overall survival; non-relapse mortality	High — synthesis only
6	What sleep data already exist unreported?	Individual-participant-data retrieval from registered orthobiologic trials holding unreported sleep instruments	Pooled sleep-instrument change	Moderate — requires sponsor cooperation
7	Can sleep endpoints be standardised in regenerative trials?	Adoption of the Sleep–Regenerative Minimum Reporting Set (10 items, see Discussion)	Reporting completeness	High — editorial and protocol adoption
8	Does melatonin act as a regenerative adjuvant in humans?	Randomised adjuvant trial of melatonin 4 mg alongside a standard orthobiologic protocol	Structural or functional healing endpoint	Moderate

Table 8: Chrono-regenerative research agenda.

CHRONO-PRP is a timing-randomised, assessor-blinded trial in symptomatic knee osteoarthritis or rotator cuff tendinopathy in which participants are randomised to morning (07:00–09:00) or evening (17:00–19:00) injection of an otherwise identical platelet-rich plasma preparation, with the primary endpoint a validated composite of pain and function at six months and secondary endpoints of matrix or imaging change and a full sleep panel. The design isolates administration phase while holding product, operator and rehabilitation constant.

HARVEST-TIME is a within-donor crossover in which autologous product is prepared from morning and evening draws in the same participants, with primary endpoints of platelet and leucocyte composition, growth-factor content, progenitor yield and clock-gene expression in the cellular fraction. It asks whether the diurnal variation shown for mobilised CD34+ cells [4] extends to the products used in musculoskeletal practice, without exposing anyone to a new intervention.

SLEEP-PRIME is a factorial trial in which participants scheduled for an orthobiologic intervention are randomised to a brief cognitive behavioural sleep intervention or usual care before the procedure, crossed with morning or evening administration. Primary endpoints are function and pain at six and twelve months; mechanistic secondary endpoints are inflammatory tone, and a full sleep panel. This is the design that would test the central clinical claim of the Circadian–Regenerative Interface model: that sleep is a modifiable determinant of regenerative outcome.

Alongside these, four syntheses are immediately feasible and currently missing: a meta-analysis of sleep and fracture or tendon healing, a meta-analysis of time-of-day of cell-graft infusion pooling the haematopoietic cohorts, a meta-analysis of sleep interventions on muscle-damage and recovery biomarkers, and an individual-participant-data analysis of the registered orthobiologic trials that already hold unreported sleep data.

We also propose the Sleep–Regenerative Minimum Reporting Set for regenerative trials, comprising ten items: (1) time of day of harvest, with clock time; (2) time of day of administration, with clock time; (3) participant chronotype; (4) habitual sleep duration; (5) a validated sleep-quality instrument at baseline and at each follow-up; (6) screening status and result for obstructive sleep apnoea; (7) shift-work status; (8) hypnotic, melatonin and sedative use; (9) any sleep intervention delivered during follow-up; and (10) the pre-specified analysis plan for sleep endpoints, including a commitment to report null results. Items 1 and 2 alone would make retrospective timing analyses possible across the entire field within a single publication cycle.

Strengths and limitations

The strengths of this review are its bidirectional scope within one appraisal framework, its verbatim extraction rule with explicit labelling of unavailable values, its tiering that renders absence of evidence visible, its use of registry and regulatory sources to quantify rather than assert reporting bias, and its derivation of a reproducible readiness metric with published anchors.

Several limitations require statement. First, the corrected covered area was not computed, for the reasons given in the Methods; overlap was addressed structurally and the substitution is not equivalent, so quantitative overlap remains unmeasured. Second, screening, extraction and appraisal were conducted by a single author, without duplicate independent assessment; this is an AMSTAR-2-relevant limitation of this overview itself, and readers should weight it accordingly. Third, the RCRI is an explicit heuristic with published anchors, not a validated instrument; its value is that its scoring is auditable and contestable. Fourth, umbrella reviews inherit the biases of their included syntheses, and a substantial minority of included reviews were of low or critically low AMSTAR-2 confidence, particularly in the cell-therapy literature [37]. Fifth, several domains rest on evidence in which causal direction is not established by design, notably the sleep–pain and sleep–bone associations, although Mendelian randomisation supports

causal contributions in the fracture and epigenetic-age domains [66,52]. Sixth, no registration was undertaken, which limits protection against post-hoc flexibility; the eligibility framework and instruments are therefore reported in full to allow replication. Seventh, grey literature and non-indexed registries were not systematically interrogated. Finally, the certainty of evidence in Direction 2 is uniformly low to very low, and readers should not interpret the absence of pooled effects as evidence of absence of effect; it is, in most cells of (**Table 3**), evidence of absence of measurement.

Conclusion

Sleep and regenerative medicine are coupled by circadian biology, but the evidence supporting that coupling is profoundly one-sided. Sleep disturbance, insomnia and obstructive sleep apnoea are meta-analytically associated with greater inflammatory load, lower anabolic tone, more chronic musculoskeletal pain, worse postoperative pain and complications, lower bone density, higher fracture risk and reduced physical performance, and the circadian timing of drugs, vaccines, surgery and haematopoietic grafts carries effect sizes that would be considered decisive in any other context. In the opposite direction, no meta-analysis of mesenchymal stromal cells, extracellular vesicles or platelet-rich plasma pools a single sleep endpoint in any indication; the only placebo-controlled trial with sleep as its primary endpoint was null; no exosome trial has reported a sleep outcome; and no cell or tissue-engineering intervention has been tested for obstructive sleep apnoea in humans.

Two conclusions follow with different force. Treating sleep as a modifiable determinant of regenerative outcome — phenotyping it, treating insomnia before intervention, managing obstructive sleep apnoea perioperatively, and documenting the clock time of harvest and administration — is already defensible on existing evidence and costs the field almost nothing. Claiming that a regenerative product restores sleep is not defensible on any current human evidence, and in the case of exosome products is made in a setting of documented regulatory concern. The Circadian–Regenerative Interface model, the Regenerative Chronotherapeutic Readiness Index, the Sleep–Regenerative Minimum Reporting Set and the three chrono-randomised designs proposed here are offered as the shortest route from that asymmetry to a symmetric evidence base. The first trial to randomise the time of day of an orthobiologic injection will be testing the oldest variable in the biology of repair and the newest in its clinical practice.

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Conflict of interest

The author declares no conflict of interest. No financial or non-financial competing interests, no commercial affiliation with any manufacturer of cell, extracellular-vesicle, platelet-derived, peptide or photobiomodulation products, and no relationship with any sleep-medicine device or pharmaceutical manufacturer influenced the design, conduct, analysis, interpretation or reporting of this review.

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Author contributions

All Authors conceived the review, designed the eligibility framework and appraisal strategy, screened and selected the evidence, extracted and verified all data, performed the quality and certainty appraisals, derived the Circadian–Regenerative Interface model, the Regenerative Chronotherapeutic Readiness Index and the Sleep–Regenerative Minimum Reporting Set, and wrote and approved the manuscript.

Data availability

All data analysed in this review are contained within published articles, publicly accessible trial registry records and publicly accessible regulatory documents, each cited with its digital object identifier, PubMed identifier or uniform resource locator. The structured extraction matrix and the Regenerative Chronotherapeutic Readiness Index scoring sheet are available from the author on reasonable request.

References

1. Aznar Benitah S, Welz PS. Circadian regulation of adult stem cell homeostasis and aging. *Cell Stem Cell*. 2020;26(6):817-31.
2. Rogers EH, Hunt JA, Pekovic-Vaughan V. Adult stem cell maintenance and tissue regeneration around the clock: do impaired stem cell clocks drive age-associated tissue degeneration? *Biogerontology*. 2018;19:497-517. \
3. Mendez-Ferrer S, Lucas D, Battista M, Frenette PS. Haematopoietic stem cell release is regulated by circadian oscillations. *Nature*. 2008;452(7186):442-7.
4. Lucas D, Battista M, Shi PA, Isola L, Frenette PS. Mobilized hematopoietic stem cell yield depends on species-specific circadian timing. *Cell Stem Cell*. 2008;3(4):364-6.
5. Janich P, Pascual G, Merlos-Suarez A, Batlle E, Ripperger J, Albrecht U, et al. The circadian molecular clock creates epidermal stem cell heterogeneity. *Nature*. 2011;480(7376):209-14.
6. Zhu P, Hamlish NX, Thakkar AV, Steffek AWT, Rendleman EJ, Khan NH, et al. BMAL1 drives muscle repair through control of hypoxic NAD⁺ regeneration in satellite cells. *Genes Dev*. 2022;36(3-4):149-66.
7. Chang J, Garva R, Pickard A, Yeung CYC, Mallikarjun V, Swift J, et al. Circadian control of the secretory pathway maintains collagen homeostasis. *Nat Cell Biol*. 2020;22(1):74-86.
8. Mobjerg A, Pedersen SD, Kjaer M, Yeung CY. Role of the tendon circadian clock in tendinopathy and implications for therapeutics. *Int J Exp Pathol*. 2025;106(3):e70001.
9. Boucher H, Vanneaux V, Domet T, Parouchev A, Larghero J. Circadian clock genes modulate human bone marrow mesenchymal stem cell differentiation, migration and cell cycle. *PLoS One*. 2016;11(1):e0146674.
10. Moradi S, Nouri M, Moradi MT, Khodarahmi R, Zarrabi M, Khazaie H. The mutual impacts of stem cells and sleep: opportunities for improved stem cell therapy. *Stem Cell Res Ther*. 2025;16(1):157.
11. Alnasser SM. A review of the circadian regulation of stem cells: harnessing the internal body clock for enhanced regenerative therapies. *Stem Cell Res Ther*. 2026;17:165.
12. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc*. 2015;13(3):132-40.
13. Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H, Tungpunkom P. Umbrella reviews. In: Aromataris E, Lockwood C, Porritt K, Pilla B, Jordan Z, editors. *JBIManual for Evidence Synthesis*. Adelaide: JBI; 2024.
14. Pollock M, Fernandes RM, Becker LA, Pieper D, Hartling L. Chapter V: overviews of reviews. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.5. London: Cochrane; 2024.
15. Gates M, Gates A, Pieper D, Fernandes RM, Tricco AC, Moher D, et al. Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. *BMJ*. 2022;378:e070849.
16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
17. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
18. JBI. Checklist for systematic reviews and research syntheses. Adelaide: JBI; 2020.
19. Whiting P, Savovic J, Higgins JPT, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol*. 2016;69:225-34.
20. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-6.
21. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-94.
22. Runge N, Ahmed I, Saueressig T, Perea J, Labie C, Mairesse O, et al. The bidirectional relationship between sleep problems and chronic musculoskeletal pain: a systematic review with meta-analysis. *Pain*. 2024;165(11):2455-67.
23. Santos M, Gabani FL, de Andrade SM, Bizzozero-Peroni B, Martinez-Vizcaino V, Gonzalez AD, et al. The bidirectional association between chronic musculoskeletal pain and sleep-related problems: a systematic review and meta-analysis. *Rheumatology*. 2023;62(9):2951-62.
24. Chan YH, Teo CB, Tay JK, Cheong CS. The association between obstructive sleep apnea and osteoporosis: a systematic review and meta-analysis. *Sleep Med Rev*. 2024;78:102006.

25. Wang XY, Wang XY, Liao ZX, Zhao YA, Wei C, Gong LJ. Association between obstructive sleep apnea and low bone mass in adults: a systematic review and meta-analysis. *Sleep Biol Rhythms*. 2023;22(1):65-73.
26. Craven J, McCartney D, Desbrow B, Sabapathy S, Bellinger P, Roberts L, et al. Effects of acute sleep loss on physical performance: a systematic and meta-analytical review. *Sports Med*. 2022;52(11):2669-90.
27. Kong Y, Yu B, Guan G, Wang Y, He H. Effects of sleep deprivation on sports performance and perceived exertion in athletes and non-athletes: a systematic review and meta-analysis. *Front Physiol*. 2025;16:1544286.
28. Mesas AE, Nunez de Arenas-Arroyo S, Martinez-Vizcaino V, Garrido-Miguel M, Fernandez-Rodriguez R, Bizzozero-Peroni B, et al. Is daytime napping an effective strategy to improve sport-related cognitive and physical performance and reduce fatigue? A systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med*. 2023;57(7):417-26.
29. Pieper D, Antoine SL, Mathes T, Neugebauer EAM, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol*. 2014;67(4):368-75.
30. Lunny C, Pieper D, Thabet P, Kanji S. Managing overlap of primary study results across systematic reviews: practical considerations for authors of overviews of reviews. *BMC Med Res Methodol*. 2021;21:140.
31. Kent D, Stanley J, Aurora RN, Levine CG, Gottlieb DJ, Spann MD, et al. Referral of adults with obstructive sleep apnea for surgical consultation: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. 2021;17(12):2507-31.
32. Brasil, Conselho Nacional de Saude. Resolucao no 510, de 7 de abril de 2016. *Diario Oficial da Uniao*. 2016 May 24;(98), Section 1:44-6.
33. Journal of Stem Cell Research. Aims, scope and author guidelines. Genesis Scientific Publications; ISSN 2582-8797. Available from: <https://www.genesispub.org/jscr>
34. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry*. 2016;80(1):40-52.
35. Niklasson A, Finan PH, Smith MT, Forsberg A, Dietz N, Kander T, et al. The relationship between preoperative sleep disturbance and acute postoperative pain control: a systematic review and meta-analysis. *Sleep Med Rev*. 2025;79:102014.
36. Thomas TL, Rampam S, Nithagon P, Goh GS. Increased risk of postoperative complications in patients who have obstructive sleep apnea undergoing total joint arthroplasty: a systematic review and meta-analysis. *J Arthroplasty*. 2024;39(12):3119-3127.e1.
37. Shang Z, Wang M, Zhang B, Wang X, Wanyan P. Clinical translation of stem cell therapy for spinal cord injury still premature: results from a single-arm meta-analysis based on 62 clinical trials. *BMC Med*. 2022;20:284.
38. Ballesio A, Fiori V, Lombardo C. Effects of experimental sleep deprivation on peripheral inflammation: an updated meta-analysis of human studies. *J Sleep Res*. 2025;35(1):e70099.
39. Fiori V, Ballesio A. Can cognitive behavioral therapy for insomnia (CBT-I) reduce biomarkers of inflammation? A systematic review of randomized controlled trials. *Behav Sleep Med*. 2026:1-15.
40. Savin KL, Clark TL, Perez-Ramirez P, Allen TS, Tristao Parra M, Gallo LC. The effect of cognitive behavioral therapy for insomnia (CBT-I) on cardiometabolic health biomarkers: a systematic review of randomized controlled trials. *Behav Sleep Med*. 2023;21(6):671-94.
41. Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in health and disease. *Physiol Rev*. 2019;99(3):1325-80.
42. Su L, Zhang SZ, Zhu J, Wu J, Jiao YZ. Effect of partial and total sleep deprivation on serum testosterone in healthy males: a systematic review and meta-analysis. *Sleep Med*. 2021;88:267-73.
43. Lamon S, Morabito A, Arentson-Lantz E, Knowles O, Vincent GE, Condo D, et al. The effect of acute sleep deprivation on skeletal muscle protein synthesis and the hormonal environment. *Physiol Rep*. 2021;9(1):e14660.
44. Van Cauter E, Plat L. Physiology of growth hormone secretion during sleep. *J Pediatr*. 1996;128(5 Pt 2):S32-7.
45. Smith TJ, Wilson MA, Karl JP, Orr J, Smith CD, Cooper AD, et al. Impact of sleep restriction on local immune response and skin barrier restoration with and without multinutrient nutrition intervention. *J Appl Physiol*. 2018;124(1):190-200.
46. Das A, Gupta R, Huda F, Kumar N, Krishnan V, Basu S. Effect of sleep quality on wound healing among patients undergoing emergency laparotomy: an observational study. *J Clin Sleep Med*. 2025;21(3):503-12.
47. Mostaghimi L, Obermeyer WH, Ballamudi B, Martinez-Gonzalez D, Benca RM. Effects of sleep deprivation on wound healing. *J Sleep Res*. 2005;14(3):213-9.
48. Landis CA, Whitney JD. Effects of 72 hours sleep deprivation on wound healing in the rat. *Res Nurs Health*. 1997;20(3):259-67.
49. Xu X, Wang R, Sun Z, Wu R, Yan W, Jiang Q, et al. Trehalose enhances bone fracture healing in a rat sleep deprivation model. *Ann Transl Med*. 2019;7(14):297.
50. Fostitsch AJ, Schwarzer G, Buchgeister M, Surbeck W, Lahmann C, Spiegelhalter K, et al. The association between sleep quality and telomere attrition: a systematic review and meta-analysis comprising 400,212 participants. *Sleep Med Rev*. 2025;80:102073.
51. Sabot D, Lovegrove R, Stapleton P. The association between sleep quality and telomere length: a systematic literature review. *Brain Behav Immun Health*. 2023;28:100577.
52. Zhao W, Yu S, Xu Y, Liao H, Chen D, Lu T, et al. Sleep traits causally affect epigenetic age acceleration: a Mendelian randomization study. *Sci Rep*. 2025;15:7439.
53. Rivero-Segura NA, Rodriguez Cuartas JD, Garcia-delaTorre P, Sanchez-Garcia S, Ramirez-Aldana R, Gomez-Verjan JC. Insomnia accelerates the epigenetic clocks in older adults. *GeroScience*. 2025;47(6):6777-88.
54. Neculicioiu VS, Colosi IA, Costache C, Toc DA, Sevastre-Berghian A, Colosi HA, et al. Sleep deprivation-induced oxidative stress in rat models: a scoping systematic review. *Antioxidants (Basel)*. 2023;12(8):1600.
55. Villafuerte G, Miguel-Puga A, Rodriguez EM, Machado S, Manjarrez E, Arias-Carrion O. Sleep deprivation and oxidative stress in animal models: a systematic review. *Oxid Med Cell Longev*. 2015;2015:234952.
56. Ullern H, Schnur P, Boccara CN, Knaevelsrud H. Rest, repair, repeat: the complex relationship of autophagy and sleep. *J Mol Biol*. 2025;437(18):169227.
57. Carroll JE, Prather AA. Sleep and biological aging: a short review. *Curr Opin Endocr Metab Res*. 2021;18:159-64.
58. Silva S, Hayden JA, Mendes G, Verhagen AP, Pinto RZ, Silva A. Sleep as a prognostic factor in low back pain: a systematic review of prospective cohort studies and secondary analyses of randomized controlled trials. *Sleep*. 2024;47(5):zsae023.

59. Panigrahi A, Sahu P, Mohanty SS, Dandana RS, Sahani JJ, Pati S. Sleep disturbances and sleep quality among individuals diagnosed with osteoarthritis: a systematic review and meta-analysis. *Front Med.* 2025;12:1653047.
60. Varallo G, Giusti EM, Manna C, Castelnuovo G, Piza F, Franceschini C, et al. Sleep disturbances and sleep disorders as risk factors for chronic postsurgical pain: a systematic review and meta-analysis. *Sleep Med Rev.* 2022;63:101630.
61. Whale K, Dennis J, Wyde V, Beswick A, Goberman-Hill R. The effectiveness of non-pharmacological sleep interventions for people with chronic pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord.* 2022;23(1):440.
62. Bjurström MF, Irwin MR, Bodelsson M, Smith MT, Mattsson-Carligen N. Preoperative sleep quality and adverse pain outcomes after total hip arthroplasty. *Eur J Pain.* 2021;25(7):1482-92.
63. Driesman AS, Montgomery WC, Kleeman-Forsthuber LT, Johnson RM, Dennis DA, Jennings JM. Perioperative sleep quality disturbances in total joint arthroplasty is multifactorial. *J Arthroplasty.* 2024;39(6):1474-9.
64. Pettit RJ, Gregory B, Stahl S, Buller LT, Deans C. Total joint arthroplasty and sleep: the state of the evidence. *Arthroplast Today.* 2024;27:101383.
65. Tian J, Zhang J, Ding L, Qi X. Association between sleep duration and low bone mineral density and osteoporosis: a systematic review and meta-analysis. *Calcif Tissue Int.* 2024;116(1):3.
66. Qian Y, Xia J, Liu KQ, Xu L, Xie SY, Chen GB, et al. Observational and genetic evidence highlight the association of human sleep behaviors with the incidence of fracture. *Commun Biol.* 2021;4:1339.
67. Pan F, Tian J, Cicuttini F, Jones G. Sleep disturbance and bone mineral density, risk of falls and fracture: results from a 10.7-year prospective cohort study. *Bone.* 2021;147:115938.
68. Yang D, Xiang C, Wang T, Guo X, Ouyang Z, Wang L. Association between night shift work and risk of osteoporosis and osteoporosis-related pathological fracture. *Front Public Health.* 2026;13:1719807.
69. Wang Q, Wu Q, Feng J, Sun X. Obstructive sleep apnea and endothelial progenitor cells. *Patient Prefer Adherence.* 2013;7:1077-90.
70. Lui MM, Tse HF, Mak JC, Lam JC, Lam DC, Tan KC, et al. Altered profile of circulating endothelial progenitor cells in obstructive sleep apnea. *Sleep Breath.* 2013;17(3):937-42.
71. Simpson PJL, Hoyos CM, Celermajer D, Liu PY, Ng MKC. Effects of continuous positive airway pressure on endothelial function and circulating progenitor cells in obstructive sleep apnoea: a randomised sham-controlled study. *Int J Cardiol.* 2013;168(3):2042-8.
72. Prabhakar NR, Peng YJ, Nanduri J. Hypoxia-inducible factors and obstructive sleep apnea. *J Clin Invest.* 2020;130(10):5042-51.
73. Lastella M, Halson SL, Vitale JA, Memon AR, Vincent GE. To nap or not to nap? A systematic review evaluating napping behavior in athletes and the impact on various measures of athletic performance. *Nat Sci Sleep.* 2021;13:841-62.
74. Silva AC, Silva A, Edwards BJ, Tod D, Amaral AS, de Alcantara Borba D, et al. Sleep extension in athletes: what we know so far - a systematic review. *Sleep Med.* 2021;77:128-35.
75. Cunha LA, Costa JA, Marques EA, Brito J, Lastella M, Figueiredo P. The impact of sleep interventions on athletic performance: a systematic review. *Sports Med Open.* 2023;9(1):58.
76. Dobrosielski DA, Sweeney L, Lisman PJ. The association between poor sleep and the incidence of sport and physical training-related injuries in adult athletic populations: a systematic review. *Sports Med.* 2021;51(4):777-93.
77. Inoue S, Tsuboi I, Miszczek M, Miyajima K, Roessler N, Alfharhan AR, et al. Time-of-day immunotherapy administration and outcomes in advanced cancers: a systematic review and meta-analysis. *JAMA Netw Open.* 2026;9(5):e2610815.
78. Vink K, Kusters J, Wallinga J. Chrono-optimizing vaccine administration: a systematic review and meta-analysis. *Front Public Health.* 2025;13:1516523.
79. Yang N, Elmatite WM, Elgallad A, Gajdos C, Pourafkari L, Nader ND. Patient outcomes related to the daytime versus after-hours surgery: a meta-analysis. *J Clin Anesth.* 2019;54:13-8.
80. Yao YT, Huang S, Chao M. The effects of daytime variation on short-term outcomes of cardiac surgical patients: a PRISMA-compliant systematic review and meta-analysis. *J Cardiothorac Vasc Anesth.* 2026;40(2):492-500.
81. Xie Z, Zhang J, Wang C, Yan X. Chronotherapy for morning blood pressure surge in hypertensive patients: a systematic review and meta-analysis. *BMC Cardiovasc Disord.* 2021;21(1):274.
82. Bernardi C, Pradier A, Masouridi-Levrat S, Morin S, Mamez AC, Giannotti F, et al. Influence of time-of-day of graft infusion on allogeneic hematopoietic stem cell transplantation outcomes: a validation cohort study. *J Immunother Cancer.* 2025;13(12):e013372.
83. Teng Y, Zhao X, Liu A. Circadian rhythm-guided cellular therapy in hematologic malignancies: mechanisms, clinical evidence, and optimization strategies. *Biomark Res.* 2026;14:79.
84. Grgic J, Lazinica B, Garofolini A, Schoenfeld BJ, Saner NJ, Mikulic P. The effects of time of day-specific resistance training on adaptations in skeletal muscle hypertrophy and muscle strength: a systematic review and meta-analysis. *Chronobiol Int.* 2019;36(4):449-60.
85. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. *PLoS One.* 2013;8(5):e63773.
86. Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A, et al. Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med Rev.* 2005;9(1):41-50.
87. Cruz-Sanabria F, Bruno S, Crippa A, Frumento P, Scarselli M, Skene DJ, et al. Optimizing the time and dose of melatonin as a sleep-promoting drug: a systematic review of randomized controlled trials and dose-response meta-analysis. *J Pineal Res.* 2024;76(5):e12985.
88. Pejón TMM, Messias LHD, Nascimento RHO, Bertolucci V, Ninomiya AF, Beck WR. Melatonin administration on bone properties of animals under hypoestrogenism: a systematic review. *Rev Endocr Metab Disord.* 2025;26(2):279-91.
89. Hardeland R. Melatonin and the programming of stem cells. *Int J Mol Sci.* 2022;23(4):1971.
90. Sohn EH, Kim SN, Lee SR. Melatonin's impact on wound healing. *Antioxidants (Basel).* 2024;13(10):1197.
91. Li S, Si H, Xu J, Liu Y, Shen B. The therapeutic effect and mechanism of melatonin on osteoarthritis: from the perspective of non-coding RNAs. *Front Genet.* 2022;13:968919.
92. Du J, Tan Y. A systematic review and meta-analysis of randomized controlled trials investigating the effects of melatonin supplementation on bone mineral density, quality of life, and sleep in menopausal women. *Front Nutr.* 2026;13:1687221.

93. Gao W, Li R, Ye M, Zhang L, Zheng J, Yang Y, et al. The circadian clock has roles in mesenchymal stem cell fate decision. *Stem Cell Res Ther.* 2022;13(1):200.
94. Putthanbut N, Su PAB, Lee JY, Borlongan CV. Circadian rhythms in stem cells and their therapeutic potential. *Stem Cell Res Ther.* 2025;16:85.
95. Parasram K, Karpowicz P. Time after time: circadian clock regulation of intestinal stem cells. *Cell Mol Life Sci.* 2020;77(7):1267-88.
96. Ruby CL, Major RJ, Hinrichsen RD. Regulation of tissue regeneration by the circadian clock. *Eur J Neurosci.* 2021;53(11):3576-97.
97. Cao M, Ou Y, Zhang J, Wang H, Liu Y, Chen Y, et al. Efficacy and safety of mesenchymal stem cells in the treatment of knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Stem Cell Res Ther.* 2025;16(1):122.
98. Tian X, Qu Z, Cao Y, Zhang B. Relative efficacy and safety of mesenchymal stem cells for osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne).* 2024;15:1366297.
99. Islam MA, Alam SS, Kundu S, Ahmed S, Sultana S, Patar A, et al. Mesenchymal stem cell therapy in multiple sclerosis: a systematic review and meta-analysis. *J Clin Med.* 2023;12(19):6311.
100. Khan I, Rehman U, Aslam F, Khan S, Bhatti U, Ramzan H, et al. Efficacy and safety of mesenchymal stromal cells for steroid-refractory acute graft-versus-host disease: an updated meta-analysis of randomized controlled trials. *Stem Cell Rev Rep.* 2025;21(7):1997-2009.
101. Weiss DJ, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. *Chest.* 2013;143(6):1590-8.
102. ClinicalTrials.gov. A study of allogeneic HB-adMSCs for the treatment of chronic post-COVID-19 syndrome (NCT05126563): posted results. Bethesda (MD): US National Library of Medicine.
103. Vij R, Kim H, Park H, Cheng T, Lotfi D, Chang D. Adipose-derived, autologous mesenchymal stem cell therapy for patients with post-COVID-19 syndrome: an intermediate-size expanded access program. *Stem Cell Res Ther.* 2023;14:287.
104. Mokhmer SA, Desouky MK, Abdelghany AK, Ibrahim MFG. Stem cells therapeutic effect in a reserpine-induced fibromyalgia rat model: a possible NLRP3 inflammasome modulation with neurogenesis promotion in the cerebral cortex. *Life Sci.* 2023;325:121784.
105. Inami N. Intravenous administration of human-derived mesenchymal stem cell-conditioned medium for patients with general malaise. *J Clin Med.* 2025;14(16):5884.
106. ClinicalTrials.gov. HB-adMSCs for the treatment of Parkinson's disease (NCT04928287): posted results. Bethesda (MD): US National Library of Medicine.
107. ClinicalTrials.gov. Allogeneic HB-adMSCs for the treatment of Parkinson's disease (NCT04995081): posted results. Bethesda (MD): US National Library of Medicine.
108. ClinicalTrials.gov. Autologous mesenchymal stem cells for Parkinson's disease (NCT04146519). Bethesda (MD): US National Library of Medicine. Available from: <https://clinicaltrials.gov/study/NCT04146519>
109. ClinicalTrials.gov. ATCell for post-concussion syndrome (NCT04744051). Bethesda (MD): US National Library of Medicine.
110. Cox CS Jr, Ashley JR, Juraneck J, Ewing-Cobbs L, Prossin AR, Pedroza C, et al. Autologous adipose-derived mesenchymal stromal cells for chronic traumatic brain injury. *Brain.* 2026;awag165.
111. Uwishema O, Ghezzi M, Wojtara M, Esene IN, Obamiro K. Stem cell therapy use in patients with dementia: a systematic review. *Int J Emerg Med.* 2025;18:95.
112. Feizi H, Hosseini MS, Seyed-Sahebari S, Karimi H, Mosaddeghi-Heris R, Sadigh-Eteghad S, et al. A systematic review of clinical efficacy and safety of cell-based therapies in Alzheimer's disease. *Dement Neuropsychol.* 2024;18:e20240147.
113. Osanai T, Houkin K, Uchiyama S, Minematsu K, Taguchi A, Terasaka S. Efficacy and safety of stem cell therapy for acute and subacute ischemic stroke: a systematic review and meta-analysis. *Sci Rep.* 2025;15.
114. Santos B, Ramalho B, Relógio A, Cavadas C, Gaspar LS, Alvaro AR. Systematic review of changes in extracellular vesicles associated with obstructive sleep apnoea: implications for diagnosis and treatment. *Eur Respir Rev.* 2025;34(178):250073.
115. Zhang M, Du Y, Chen L, Tang Q, Liu C, Li N, et al. Genome-wide, integrative analysis implicates exosome-derived microRNA dysregulation in chronic insomnia. *Sleep.* 2025;48(6):zsaf051.
116. Lin Y, Kang Z, Su C, Li S, Xie W. Extracellular vesicles ameliorate sleep deprivation induced anxiety-like behavior and cognitive impairment in mice. *Mol Ther Methods Clin Dev.* 2024;32(1):101207.
117. Gu X, Zhu J. Roles of exosomes and exosomal microRNAs in postoperative sleep disturbance. *Nat Sci Sleep.* 2021;13:1363-75.
118. Kawikova I, Spicka V, Lai JCK, Askenase PW, Wen L, Kejik Z, et al. Extracellular vesicles as precision therapeutics for psychiatric conditions: targeting interactions among neuronal, glial, and immune networks. *Front Immunol.* 2025;16:1454306.
119. ClinicalTrials.gov. Zofin for COVID-19 long haulers (NCT05228899). Bethesda (MD): US National Library of Medicine.
120. US Food and Drug Administration. Public safety notification on exosome products. Silver Spring (MD): FDA; 2019 Dec 6.
121. US Food and Drug Administration. Public safety alert due to marketing of unapproved stem cell and exosome products. Silver Spring (MD): FDA; 2019 Dec 9.
122. Turner L, Munsie M, Levine AD, Master Z. Businesses marketing purported stem cell treatments and exosome therapies for COVID-19: an analysis of direct-to-consumer online advertising claims. *Stem Cell Reports.* 2023.
123. Nanos G, Silva M, Patel C. Effects of ExoTMS stimulation on sleep quality: a sham-controlled study. *Sleep Sci Pract.* 2026;10:25.
124. Belk JW, Kraeutler MJ, Houck DA, Goodrich JA, Dragoo JL, McCarty EC. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Am J Sports Med.* 2021;49(1):249-60.
125. Xiong Y, Gong C, Peng X, Liu X, Su X, Tao X, et al. Comparison of the efficacy of platelet-rich plasma injections for osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Front Med (Lausanne).* 2023;10:1204144.
126. Li S, Wu T. Effect of platelet-rich plasma on knee, hip and traumatic osteoarthritis: a meta-analysis and systematic review. *BMC Musculoskelet Disord.* 2026;27:183.
127. Pei X, Wang H, Zhang J, Sun Y, Li X. Platelet-rich plasma therapy for low back pain: a systematic review and meta-analysis. *J Back Musculoskelet Rehabil.* 2026;10538127261448983.
128. Lin MT, Wei KC, Wu CH. Effectiveness of platelet-rich plasma injection in rotator cuff tendinopathy: a systematic review and meta-analysis of randomized controlled trials. *Diagnostics (Basel).* 2020;10(4):189.

129. ClinicalTrials.gov. Low-dose versus high-dose platelet-rich plasma for glenohumeral osteoarthritis (NCT05675527). Bethesda (MD): US National Library of Medicine.
130. ClinicalTrials.gov. Platelet-rich plasma versus corticosteroid versus saline in rotator cuff tendinopathy (NCT05603468). Bethesda (MD): US National Library of Medicine.
131. ClinicalTrials.gov. Platelet-rich plasma, platelet-poor plasma and bone marrow aspirate concentrate in hip arthroscopy (NCT06003101). Bethesda (MD): US National Library of Medicine.
132. ClinicalTrials.gov. Autologous adipose-derived mesenchymal stem cells for knee osteoarthritis after high tibial osteotomy (NCT03000712). Bethesda (MD): US National Library of Medicine.
133. Weikel JC, Wichniak A, Ising M, Brunner H, Friess E, Held K, et al. Ghrelin promotes slow-wave sleep in humans. *Am J Physiol Endocrinol Metab*. 2003;284(2):E407-15.
134. Copinschi G, Leproult R, Van Onderbergen A, Caufriez A, Cole KY, Schilling LM, et al. Prolonged oral treatment with MK-677, a novel growth hormone secretagogue, improves sleep quality in man. *Neuroendocrinology*. 1997;66(4):278-86.
135. Perras B, Marshall L, Kohler G, Born J, Fehm HL. Sleep and endocrine changes after intranasal administration of growth hormone-releasing hormone in young and aged humans. *Psychoneuroendocrinology*. 1999;24(7):743-57.
136. Morselli LL, Nedeltcheva A, Leproult R, Spiegel K, Martino E, Legros JJ, et al. Impact of growth hormone replacement therapy on sleep in adult patients with growth hormone deficiency of pituitary origin. *Eur J Endocrinol*. 2013;168(5):763-70.
137. 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 beta4 in healthy Chinese volunteers. *J Cell Mol Med*. 2021;25(17):8222-8.
138. 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(12):611-9.
139. Vasireddi N, Hahamyam 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(4):485-95.
140. Xue T, Wu X, Chen S, Yang Y, Yan Z, Song Z, et al. The efficacy and safety of dual orexin receptor antagonists in primary insomnia: a systematic review and network meta-analysis. *Sleep Med Rev*. 2022;61:101573.
141. Kishi T, Ikuta T, Citrome L, Sakuma K, Hatano M, Hamanaka S, et al. Comparative efficacy and safety of daridorexant, lemborexant, and suvorexant for insomnia: a systematic review and network meta-analysis. *Transl Psychiatry*. 2025;15(1):211.
142. de Azevedo WMV, de Souza K, Defante ML, Salgado ASI, Lopes-Martins RAB, Gomes da Silva S, et al. Photobiomodulation and sleep quality: systematic review and meta-analysis. *Lasers Med Sci*. 2026;41(1):122.
143. Gaggi NL, Parincu Z, Peterson A, O'Brien C, Kam K, Tural U, et al. Enhancing sleep, wakefulness, and cognition with transcranial photobiomodulation: a systematic review. *Front Behav Neurosci*. 2025;19:1542462.
144. Alvarez-Martinez M, Borden G. A systematic review on whole-body photobiomodulation for exercise performance and recovery. *Lasers Med Sci*. 2025;40:55.
145. Yeh SW, Hong CH, Shih MC, Tam KW, Huang YH, Kuan YC. Low-level laser therapy for fibromyalgia: a systematic review and meta-analysis. *Pain Physician*. 2019;22(3):241-54.
146. Fitzmaurice BC, Heneghan NR, Rayen ATA, Grenfell RL, Soundy AA. Whole-body photobiomodulation therapy for fibromyalgia: a feasibility trial. *Behav Sci (Basel)*. 2023;13(9):717.
147. Ji Q, Yan S, Ding J, Zeng X, Liu Z, Zhou T, et al. Photobiomodulation improves depression symptoms: a systematic review and meta-analysis of randomized controlled trials. *Front Psychiatry*. 2024;14:1267415.
148. Doenya-Barak K, Elman Shina K, Lang E, Finci S, Elkarif V, Shorer R, et al. The effect of hyperbaric oxygen therapy on sleep quality across diverse patient populations. *Front Neurol*. 2026;17:1690633.
149. Hadanny A, Zilberman-Itskovich S, Catalogna M, Elman-Shina K, Lang E, Finci S, et al. Long term outcomes of hyperbaric oxygen therapy in post covid condition: longitudinal follow-up of a randomized controlled trial. *Sci Rep*. 2024;14:3604.
150. Cain T, Brinsley J, Bennett H, Nelson M, Maher C, Singh B. Effects of cold-water immersion on health and wellbeing: a systematic review and meta-analysis. *PLoS One*. 2025;20(1):e0317615.
151. Ding WH, Liu YH, Li XY, Wang L, Zhao Y, Chen X. Dental pulp stem cells promote genioglossus repair and systemic amelioration in chronic intermittent hypoxia. *iScience*. 2024;27(11):111143.
152. Jakobsen KJ, Gronhoj C, Jensen DH, Fischer-Nielsen A, Hjulster T, von Buchwald C. Mesenchymal stem cell therapy for laryngotracheal stenosis: a systematic review of preclinical studies. *PLoS One*. 2017;12(9):e0185283.
153. Braun M, Stoerzel M, Wollny M, Schoebel C, Sommer JU, Heiser C. Patient-reported outcomes with hypoglossal nerve stimulation for treatment of obstructive sleep apnea: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2023;280:4627-39.
154. Kim DH, Kim SW, Han JS, Kim GJ, Basurrah MA, Hwang SH. Hypoglossal nerve stimulation effects on obstructive sleep apnea over time: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2024;170(3):736-46.
155. Kent DT, Carden KA, Wang L, Lindsell CJ, Ishman SL. Evaluation of hypoglossal nerve stimulation treatment in obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg*. 2019;145(11):1044-52.
156. Saba ES, Kim H, Huynh P, Jiang N. Orofacial myofunctional therapy for obstructive sleep apnea: a systematic review and meta-analysis. *Laryngoscope*. 2024;134(1):480-95.
157. Camacho M, Certal V, Abdullatif J, Zaghi S, Ruoff CM, Capasso R, et al. Myofunctional therapy to treat obstructive sleep apnea: a systematic review and meta-analysis. *Sleep*. 2015;38(5):669-75.
158. Xie Y, Liu S, Chen XJ, Yu HH, Yang Y, Wang W. Effects of exercise on sleep quality and insomnia in adults: a systematic review and meta-analysis of randomized controlled trials. *Front Psychiatry*. 2021;12:664499.
159. Imamura M, Robertson C, Hudson J, Whibley D, Aucott L, Gillies K, et al. Effects of pharmacological and non-pharmacological interventions for the management of sleep problems in people with fibromyalgia: a multi-methods evidence synthesis. *Health Technol Assess*. 2025;29(20):1-228.
160. Cintron D, Lipford M, Larrea-Mantilla L, Spencer-Bonilla G, Lloyd R, Gionfriddo MR, et al. Efficacy of menopausal hormone therapy on sleep quality: systematic review and meta-analysis. *Endocrine*. 2017;55(3):702-11.

161. Shi PA, Isola LM, Gabrilove JL, Moshier EL, Godbold JH, Miller LK, et al. Prospective cohort study of the circadian rhythm pattern in allogeneic sibling donors undergoing standard granulocyte colony-stimulating factor mobilization. *Stem Cell Res Ther.* 2013;4(2):30.