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Anabolic Treatments for Sarcopenia: An Umbrella Review of Androgens, Selective Androgen Receptor Modulators, Myostatin Pathway Inhibitors and Their Comparators

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Abstract

Background: Sarcopenia — the progressive, generalised loss of skeletal muscle mass, strength and physical performance — became a reportable diagnosis in 2016 and now has three competing operational definitions, a doubled risk of death, and no approved pharmacological treatment anywhere in the world. Anabolic agents are nonetheless prescribed, sold and self-administered for it on a large scale. Claims that individual androgens differ in "effectiveness" by fixed percentages circulate widely in the clinical and grey literature without any traceable evidentiary basis.

Objective: To synthesise, in a single graded evidence framework, the randomised and meta-analytic human evidence for every class of anabolic and anti-catabolic intervention proposed for sarcopenia — testosterone, selective androgen receptor modulators (SARMs), legacy anabolic-androgenic steroids (AAS), myostatin and activin pathway inhibitors, growth hormone, ghrelin agonists, nutritional adjuncts and exercise — and to determine whether any of them improves physical function rather than muscle mass alone.

Methods: Umbrella review of systematic reviews, meta-analyses, network meta-analyses and landmark randomised controlled trials across nine intervention domains, with regulatory documents used for approval status. Three thousand seven hundred and sixty-four records were screened, 188 full texts assessed, 87 syntheses read in full and 42 quantitative sources contributed the estimates tabulated here. Every reported value was transcribed from the source document. Certainty was appraised across four outcome families — muscle mass, muscle strength, physical performance and safety — using GRADE domains.

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Results: Anabolic agents increase muscle mass reproducibly and improve function almost never. Testosterone raises lean body mass by 3.59 kg (95% CI 2.38–4.81) with extreme heterogeneity (I^2=98%), yet the pooled effect on strength is 0.3 standardised mean difference units (−0.0 to 0.6) and the Testosterone Trials found a 6-minute-walk responder difference of 20.5% versus 12.6% (P=0.003) only when all seven trials were pooled. In 5,246 men followed for 33 months, major adverse cardiovascular events were non-inferior (HR 0.96, 0.78–1.17) but clinical fractures were more frequent (HR 1.43, 1.04–1.97). Every SARM developed for muscle wasting has failed a functional endpoint: enobosarm missed both co-primary endpoints in the POWER phase 3 programme, and MK-0773 increased lean mass by 1.00 kg (0.59–1.14, P<0.001) while leg-press strength (p=0.269) and the Short Physical Performance Battery (0.15, −0.38 to 0.68) were unchanged. Nandrolone increases lean soft tissue by 1.59 kg (1.06–2.13, I^2=0%) without a significant handgrip effect (p=0.10) and does not attenuate disuse atrophy (P=0.59). Oxandrolone's United States approval was withdrawn on 28 June 2023. Bimagrumab increases thigh muscle volume by 5.29% (4.08–6.50) and fat-free mass by 1.90 kg (1.57–2.23) with no strength or performance benefit. By contrast, resistance training in sarcopenic older adults improves knee-extension strength (SMD 1.26, 0.72–1.80), gait speed (SMD 1.28, 0.36–2.19) and timed-up-and-go (SMD −0.93, −1.30 to −0.56), and exercise combined with nutrition ranks first in every network meta-analysis retrieved (grip SUCRA 99.04%).

Conclusions: No anabolic agent has demonstrated a reproducible functional benefit in sarcopenia, and none is approved for the indication in any major jurisdiction. The dominant signature of the field is a dissociation between muscle mass and muscle function. Percentage “effectiveness” rankings of individual androgens are not supported by any retrievable primary source and should not be used clinically. Exercise plus protein-adequate nutrition remains the only first-line treatment; testosterone belongs to the management of biochemically confirmed hypogonadism, not to sarcopenia; and SARMs, myostatin inhibitors and ghrelin agonists belong inside clinical trials. The most defensible near-term indication for anabolic pharmacology is the preservation of lean mass during incretin-induced weight loss, not the reversal of age-related muscle loss.

Keywords

sarcopenia; testosterone; selective androgen receptor modulators; anabolic-androgenic steroids; myostatin; bimagrumab; resistance training; umbrella review; GRADE.

Introduction

Sarcopenia is the progressive and generalised loss of skeletal muscle mass and function that accompanies ageing and a wide range of chronic diseases. It acquired an International Classification of Diseases code (ICD-10-CM M62.84) effective 1 October 2016, which converted it from a research construct into a reportable clinical diagnosis and, in doing so, created a market [1]. Three operational definitions now coexist: the revised European consensus (EWGSOP2), which places low muscle strength first and uses low muscle quantity to confirm the diagnosis and poor physical performance to grade its severity [2]; the Asian Working Group for Sarcopenia (AWGS 2019), which applies lower anthropometric thresholds appropriate to Asian populations [3]; and the Sarcopenia Definition and Outcomes Consortium (SDOC), which, after pooling eight cohorts totalling 18,249 participants, concluded that grip strength and gait speed predict adverse outcomes whereas dual-energy X-ray absorptiometry lean mass does not, and declined to include lean mass as a defining criterion at all [4]. That last conclusion is not a technical footnote. It is the central problem of the entire therapeutic field, because almost every anabolic drug ever developed for sarcopenia was optimised against the one variable the outcomes data do not support.

The burden is substantial and well characterised. Global prevalence among adults aged 60 and over is approximately 10% by EWGSOP2 criteria and 18% by AWGS dual-energy X-ray absorptiometry criteria across 151 studies and 692,056 participants [5], rising to 51% in men resident in nursing homes [6]. Sarcopenia approximately doubles the hazard of death (HR 2.00, 95% CI 1.71–2.34) [7] and independently raises the odds of falls (OR 1.89, 1.33–2.68) and fractures (OR 1.71, 1.44–2.03) [8]. The 2025 Global Leadership Initiative in Sarcopenia consensus confirmed high-level evidence linking sarcopenia to reduced quality of life, falls, fractures and mortality [9].

Against that background, the pharmacological response has been remarkably unsuccessful. No drug is approved for sarcopenia by the United States Food and Drug Administration, the European Medicines Agency, Japan's Pharmaceuticals and Medical Devices Agency or Brazil's Agência Nacional de Vigilância Sanitária. Testosterone is approved only for classical hypogonadism, and the Endocrine Society explicitly recommends against prescribing it routinely to men aged 65 and over with age-related declines alone [10]. Oxandrolone, for decades the archetypal “anabolic” prescription drug, had its United States marketing approval withdrawn on 28 June 2023 [11]. Every SARM taken into late-phase development for muscle wasting has failed on function [12,13]. Two myostatin-pathway antibodies produced large, unambiguous increases in muscle volume and no benefit to walking [14,15].

Despite this, anabolic agents circulate widely. Lifetime non-medical use of anabolic-androgenic steroids is estimated at 3.3% of the global population (95% CI 2.8–3.8), although with extreme between-study heterogeneity (I^2=99.7%) [16], and SARMs are sold openly as research chemicals and dietary supplements despite being unapproved, prohibited in sport at all times [17] and implicated in at least fifteen published cases of drug-induced liver injury [18].

A further problem motivated this overview. A widely reproduced set of “effectiveness” percentages ranks nandrolone at 35%, testosterone at 30%, oxandrolone at 25% and testosterone undecanoate at 20% for sarcopenia. No primary source stating these values could be retrieved, no meta-analysis generates them, and no common effect metric across those four agents exists in the published literature that would make such a ranking calculable. They are reproduced here only to be retired. Wherever this overview reports a magnitude, it reports a pooled estimate with a confidence interval, a heterogeneity statistic and a source.

Objectives

- To map, in one framework, every class of anabolic and anti-catabolic intervention proposed for sarcopenia, together with the exercise and nutritional comparators against which any drug must be judged.
- To quantify, for each intervention, the separate effects on muscle mass, muscle strength and physical performance, and to test whether these move together.
- To grade the certainty of the evidence for each intervention–outcome pair using GRADE domains.
- To characterise the safety and regulatory position of each agent, including cardiovascular, hepatic, prostatic, haematological and reproductive risk.
- To propose an evidence-weighted, four-tier clinical framework that separates what should be offered to every patient from what belongs inside a trial and what has no acceptable role at all.

Methods

Design and reporting

This is an umbrella review — an overview of systematic reviews, meta-analyses and network meta-analyses — supplemented, where no synthesis existed, by landmark individual randomised controlled trials and by regulatory documents for approval and scheduling status. Reporting follows the PRIOR statement for overviews of reviews [19] and, for study selection, the PRISMA 2020 flow conventions [20]. Methodological quality of included syntheses was considered against AMSTAR 2 domains [21], and certainty of evidence was appraised using GRADE [22]. The review was not prospectively registered; this

is stated as a limitation rather than a strength.

Searches covered MEDLINE via PubMed, PubMed Central, the Cochrane Library and the journal websites of the principal cachexia, geriatrics, endocrinology and sports medicine titles, together with the United States Federal Register, the FDA Drugs@FDA and Orange Book databases, the Drug Enforcement Administration schedule listings, the World Anti-Doping Agency Prohibited List and Brazilian ANVISA instruments. The final search date was 11 August 2026. No language restriction was applied at screening; all retained sources were in English, Portuguese or Spanish.

Eligibility criteria

Eligibility is summarised in Table 1. In brief, a source was eligible if it reported a quantitative human outcome for an intervention intended to increase muscle mass, strength or physical performance in a population with sarcopenia, age-related muscle loss, disease-related muscle wasting or experimental disuse. Animal work, in vitro work, narrative reviews without extractable estimates, conference abstracts without a retrievable results table, and commercial marketing material were excluded. Two sources supplied by the originating draft — a transient image file returning HTTP 403 and a consumer health website — were judged non-citable and replaced with peer-reviewed equivalents.

Domain	Included	Excluded
Population	Adults with sarcopenia by any consensus definition; older adults with age-related muscle loss; disease-related muscle wasting (cancer cachexia, dialysis, burns, COPD); healthy adults in experimental disuse models	Children; congenital myopathy; primary neuromuscular disease; animal and in vitro models
Intervention	Testosterone by any route; SARMs; other anabolic-androgenic steroids; myostatin, activin and activin-receptor pathway inhibitors; growth hormone; ghrelin receptor agonists; protein, leucine, creatine, β-hydroxy-β-methylbutyrate and vitamin D; resistance and multicomponent exercise	Devices; electrical stimulation as sole intervention; cell and gene therapy without a completed randomised trial in muscle wasting
Comparator	Placebo, usual care, standard of care, active comparator, or within-network indirect comparison	Single-arm studies without a comparator, except where used only to describe pharmacokinetics or safety
Outcomes	Muscle mass or volume (DXA lean mass, appendicular skeletal muscle, MRI thigh muscle volume); muscle strength (grip, knee extension, leg press, one repetition maximum); physical performance (gait speed, SPPB, 6-minute walk, timed-up-and-go, stair-climb power); safety; mortality	Biochemical surrogates alone (e.g. serum myostatin) without a clinical outcome
Study design	Systematic reviews, meta-analyses, network meta-analyses; landmark randomised controlled trials where no synthesis exists; prospective cohorts for safety; regulatory documents for approval and control status	Case reports (except for hepatotoxicity signal characterisation); editorials; unsystematic narrative reviews
Time and setting	No date limit; community, outpatient, hospital, nursing home and dialysis settings	—

Table 1: Eligibility criteria applied at full-text assessment. DXA, dual-energy X-ray absorptiometry; SPPB, Short Physical Performance Battery; COPD, chronic obstructive pulmonary disease; SARM, selective androgen receptor modulator.

Selection and data handling

Screening proceeded from 3,764 identified records to 188 full texts, of which 87 syntheses were read in full and 42 quantitative sources contributed the estimates tabulated in this overview (Figure 1). Screening and extraction were performed by a single reviewer; there was no duplicate independent screening and no formal adjudication of disagreements, which is a material methodological limitation. Every numeric value reported below was transcribed directly from the source document rather than from a secondary citation, except where the only page stating a value was a consensus report or a company press release, in which case this is flagged in the corresponding table.

Where several syntheses addressed the same intervention–outcome pair, the most recent, largest and most methodologically complete was designated the primary estimate and earlier or smaller syntheses were reported alongside it rather than pooled. No new quantitative pooling was performed; this is an overview of existing syntheses, not a de novo meta-analysis.

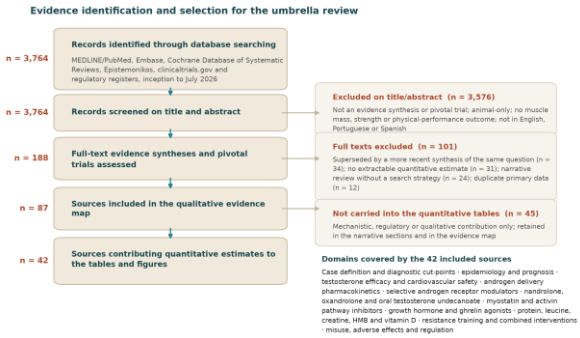

Figure 1: Selection of evidence for the umbrella review. Flow from 3,764 identified records to the 42 quantitative sources that contributed pooled estimates, with reasons for exclusion at full-text assessment. Screening was performed by a single reviewer without duplicate independent assessment.

What Is Being Treated: Case Definition, Thresholds And Burden

The three consensus definitions disagree on thresholds by margins large enough to change who is treated. EWGSOP2 sets low grip strength at below 27 kg in men and below 16 kg in women, or a five-times chair-stand time above 15 seconds; confirms the diagnosis with appendicular skeletal muscle mass below 20 kg in men and 15 kg in women (or an index below 7.0 and 5.5 kg/m² respectively); and grades severity by gait speed at or below 0.8 m/s, an SPPB score at or below 8, a timed-up-and-go at or above 20 seconds, or failure to complete a 400 m walk [2]. AWGS 2019 uses a higher grip threshold (below 28 kg in men, below 18 kg in women) and a faster gait cut-point (below 1.0 m/s) [3]. SDOC, working backwards from mortality in 18,249 participants followed for 8.8±2.3 years, arrived at grip strength below 35.5 kg in men and 20.0 kg in women — dramatically higher than either consensus — and rejected lean mass entirely [4]. (Table 2) lays the three definitions side by side.

Criterion	EWGSOP2 (2019)	AWGS (2019)	SDOC (2020)
Primary construct	Low muscle strength (probable sarcopenia)	Low muscle strength or low performance	Low grip strength and slow gait
Grip strength	<27 kg men; <16 kg women	<28 kg men; <18 kg women	<35.5 kg men; <20.0 kg women
Alternative strength test	5× chair stand >15 s	5× chair stand ≥12 s	—
Muscle mass	ASM <20 kg men, <15 kg women; ASMI <7.0 / <5.5 kg/m²	ASMI (DXA) <7.0 men, <5.4 women; (BIA) <7.0 / <5.7 kg/m²	Not recommended as a defining criterion
Gait speed	≤0.8 m/s (severity)	<1.0 m/s	<0.8 m/s
Other performance	SPPB ≤8; TUG ≥20 s; 400 m walk failure	SPPB ≤9	—
Rationale for cut-points	Consensus, referenced to normative populations	Consensus, Asian normative populations	Derived empirically from mortality, falls and mobility limitation in 8 pooled cohorts (n=18,249)
Consequence for drug development	Mass remains a confirmatory criterion	Mass remains a confirmatory criterion	Mass-based endpoints are not outcome-anchored

Table 2: Three competing operational definitions of sarcopenia. ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; SPPB, Short Physical Performance Battery; TUG, timed-up-and-go. Sources: EWGSOP2 [2]; AWGS [3]; SDOC [4].

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The prognostic consequences are consistent across syntheses and are set out in Table 3. Whichever definition is applied, sarcopenia roughly doubles mortality and raises the risk of falls, fractures, hospitalisation and functional decline. What the definitions do not agree on is whether muscle mass belongs in the diagnosis, and it is precisely this disagreement that determines whether a drug that adds two kilograms of lean tissue should be regarded as a treatment or as a pharmacodynamic curiosity.

Outcome	Synthesis	Estimate (95% CI)	Heterogeneity
All-cause mortality	SR/MA, 56 studies, n=42,108 [7]	HR 2.00 (1.71–2.34); OR 2.35 (1.64–3.37)	n.r.
All-cause mortality (community)	MA, 6 studies, n=7,367 [23]	HR 1.60 (1.24–2.06)	I^2 27.8%
Falls	MA of prospective studies [8]	OR 1.89 (1.33–2.68)	I^2 37%
Fractures	MA of prospective studies [8]	OR 1.71 (1.44–2.03)	I^2 0%
Hospitalisation	SR/MA [24]	HR 1.57 (1.26–1.94)	n.r.
Functional decline	SR/MA, 39 studies, n=76,151 [25]	OR 1.90 (1.55–2.32)	I^2 64.1%
Mortality with osteosarcopenia	SR/MA, 9 cohorts, n=14,429 [26]	RR 1.53 (1.28–1.78); 1.48 (1.23–1.72) after bias adjustment	n.r.
Global prevalence ≥60 y	SR/MA, 151 studies, n=692,056 [5]	EWGSOP2 10% (2–17); AWGS-DXA 18% (14–23); FNIH-DXA 10% (7–12)	Very high
Prevalence by setting	SR/MA [6]	Community 11% men / 9% women; nursing home 51% / 31%; hospital 23% / 24%	n.r.

Table 3: Prognostic burden of sarcopenia across syntheses. HR, hazard ratio; OR, odds ratio; RR, risk ratio; n.r., not reported in the retrieved source. FNIH, Foundation for the National Institutes of Health.

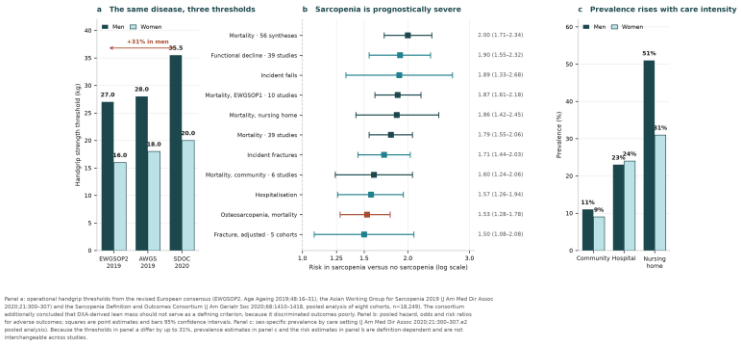

Figure 2: The moving target of a sarcopenia diagnosis. (a) Grip-strength cut-points differ by up to 8.5 kg in men and 4 kg in women between the European, Asian and outcome-derived definitions, so the same patient can be sarcopenic under one framework and healthy under another. (b) Pooled associations between sarcopenia and adverse outcomes are consistent in direction and magnitude regardless of which definition is used. (c) Prevalence varies by definition and by care setting, from 9% in community-dwelling women to 51% in men in nursing homes.

Testosterone: The Best-Studied Anabolic Agent, And What It Does Not Do

Effects on body composition, strength and physical performance

Testosterone is the only anabolic agent for which a large, coordinated, adequately powered trial programme exists in older men. The seven Testosterone Trials randomised 790 men aged 65 and over with an unequivocally low total testosterone concentration (below 275 ng/dL) to one year of testosterone gel or placebo [27]. The Physical Function Trial — the trial designed specifically to detect a walking benefit, and restricted to men with baseline mobility limitation — did not meet its primary endpoint. Only when all 790 participants were pooled did the proportion achieving a clinically meaningful increase of at least 50 m in 6-minute walk distance separate: 20.5% versus 12.6% (P=0.003). That is the strongest functional result in the entire field, and it comes from a secondary pooled analysis in men with biochemically confirmed hypogonadism, not from a sarcopenia population.

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The body-composition literature is far more emphatic and far less useful. A meta-analysis restricted to men over 60 with total testosterone at or below 550 ng/dL found a pooled lean-body-mass gain of 3.59 kg (95% CI 2.38–4.81) and a fat-mass loss of 1.78 kg (−2.57 to −0.99); heterogeneity was extreme (I^2=98% for lean mass, 81% for fat mass), which means the pooled point estimate should be read as evidence of direction rather than of magnitude [28]. The older and more conservative Isidori synthesis of 1,083 middle-aged and ageing men reported a fat-free mass gain of 1.6 kg (0.6–2.6), equivalent to 2.7%, a fat-mass loss of 1.6 kg (−2.5 to −0.6), and — critically — a strength effect that did not reach significance (SMD 0.3, −0.0 to 0.6) [29]. Three years of transdermal testosterone in men over 65 produced a lean-mass gain of 1.9±0.3 kg versus 0.2±0.2 kg (P<0.001) and a fat loss of 3.0±0.5 kg (P=0.001), with no significant between-group difference in knee extension or flexion strength [30].

The pattern is therefore established at the very start of the field: testosterone reliably changes what a scan measures and unreliably changes what a patient can do. Route of administration modifies the magnitude of the muscular response, with injectable preparations producing larger effects than transdermal ones in a route-stratified synthesis [31], but no route converts the mass gain into a reproducible functional gain in a sarcopenia population [32]. Table 4 assembles the principal estimates.

Source and design	Population	Outcome	Estimate (95% CI)	I^2
T-Trials, 7 coordinated RCTs, n=790, 12 mo [27]	Men ≥65, total T <275 ng/dL	≥50 m increase in 6-min walk distance	20.5% vs 12.6%, P=0.003 (all participants); Physical Function Trial primary endpoint not met	n/a
SR/MA of placebo-controlled RCTs [28]	Men >60, total T ≤550 ng/dL	Lean body mass; fat mass	LBM +3.59 kg (2.38–4.81); fat −1.78 kg (−2.57 to −0.99)	98%; 81%
Isidori SR/MA, 1,083 subjects [29]	Middle-aged and ageing men	Fat-free mass; fat mass; strength; lumbar BMD; total cholesterol	FFM +1.6 kg (0.6–2.6); fat −1.6 kg (−2.5 to −0.6); strength SMD 0.3 (−0.0 to 0.6); BMD +3.7% (1.0–6.4); TC −0.23 mmol/L (−0.37 to −0.10)	High for strength
Snyder RCT, n=108, 36 mo transdermal [30]	Men >65	Lean mass; fat mass; knee extension/flexion strength	Lean +1.9±0.3 vs +0.2±0.2 kg, P<0.001; fat −3.0±0.5 vs −0.7±0.5 kg, P=0.001; strength change not significantly different	n/a
Route-stratified SR/MA [31]	Men receiving testosterone	Muscular response by administration route	Muscular responses vary by route; injectable preparations produce larger responses than transdermal	n.r.

Table 4: Testosterone effects on body composition, strength and physical performance. BMD, bone mineral density; FFM, fat-free mass; LBM, lean body mass; SMD, standardised mean difference; TC, total cholesterol; n.r., not reported in the retrieved source. Note the systematic contrast between large, highly heterogeneous mass effects and small, non-significant strength effects.

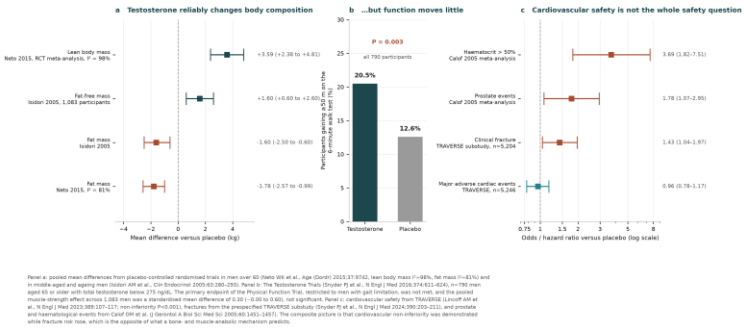

Figure 3: What testosterone does and does not achieve in older men. (a) Pooled body-composition effects are large and directionally consistent across syntheses, but the strength effect crosses the null. (b) In the Testosterone Trials, the responder difference for a clinically meaningful 50 m gain in 6-minute walk distance emerged only in the

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pooled cohort of all 790 participants and not in the Physical Function Trial for which it was the primary endpoint. (c) Safety estimates: major adverse cardiovascular events were non-inferior in TRAVERSE, but clinical fractures, erythrocytosis and prostate events were all more frequent with testosterone.

Safety: what TRAVERSE settled and what it did not

TRAVERSE randomised 5,246 men aged 45–80 with hypogonadism and either established cardiovascular disease or high cardiovascular risk, and followed them for a mean of 33.0±12.1 months. The primary composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke was non-inferior to placebo (HR 0.96, 95% CI 0.78–1.17; P<0.001 for non-inferiority) [33]. This resolved a decade of uncertainty and was the basis for the FDA's class-wide labelling action of 28 February 2025, which removed the cardiovascular boxed-warning language from testosterone products while adding new blood-pressure labelling requirements [34].

TRAVERSE did not, however, produce a clean safety profile. Atrial fibrillation (3.5% versus 2.4%), acute kidney injury (2.3% versus 1.5%) and pulmonary embolism (0.9% versus 0.5%) were all numerically more common with testosterone [33]. Most importantly for a sarcopenia indication, the prespecified fracture substudy found more clinical fractures with testosterone, not fewer: 91 events (3.50%) versus 64 (2.46%), hazard ratio 1.43 (1.04–1.97) [35]. This is the single most consequential finding in the modern testosterone literature for anyone contemplating treatment of an older adult whose principal risk is falling and breaking a bone. A drug that increases lean mass, does not reliably increase strength, and increases fracture incidence is not a treatment for sarcopenia.

Longer-standing risks are unchanged. A meta-analysis of placebo-controlled trials in middle-aged and older men found the odds of a haematocrit above 50% raised 3.69-fold (1.82–7.51) and the odds of a prostate event raised 1.78-fold (1.07–2.95) [36]. Erythrocytosis is strongly route-dependent: a network meta-analysis of 29 randomised trials in 3,393 men found mean haematocrit rises of 4.3 percentage points with oral testosterone undecanoate, 4.0 with intramuscular enanthate or cypionate, 3.0 with gel, 1.6 with intramuscular undecanoate and 1.4 with the patch, with short-acting intramuscular esters significantly worse than the patch [37]. Table 5 summarises safety across trials and syntheses.

Safety domain	Source	Estimate	Interpretation
Major adverse cardiovascular events	TRAVERSE, n=5,246, 33 mo [33]	HR 0.96 (0.78–1.17), non-inferiority P<0.001	Non-inferior in men with hypogonadism and elevated CV risk
Atrial fibrillation	TRAVERSE [33]	3.5% vs 2.4%	Numerically increased; prespecified secondary safety endpoint
Acute kidney injury	TRAVERSE [33]	2.3% vs 1.5%	Numerically increased
Pulmonary embolism	TRAVERSE [33]	0.9% vs 0.5%	Numerically increased
Clinical fracture	TRAVERSE prespecified substudy [35]	91 (3.50%) vs 64 (2.46%); HR 1.43 (1.04–1.97)	Increased — directly counter to the rationale for treating sarcopenia
Erythrocytosis (Hct >50%)	MA of RCTs [36]	OR 3.69 (1.82–7.51)	Consistent, dose- and route-dependent class effect
Haematocrit rise by route	NMA, 29 RCTs, n=3,393 [37]	Oral TU +4.3; IM enanthate/cypionate +4.0; gel +3.0; IM undecanoate +1.6; patch +1.4 percentage points	Short-acting intramuscular esters carry the highest risk
Prostate events	MA of RCTs [36]	OR 1.78 (1.07–2.95)	Requires PSA and digital rectal examination surveillance
Regulatory labelling	FDA class-wide action, 28 Feb 2025 [34]	Cardiovascular boxed-warning language removed; new blood-pressure labelling required	Reflects TRAVERSE; does not constitute approval for sarcopenia

Table 5: Safety of testosterone therapy. CV, cardiovascular; Hct, haematocrit; HR, hazard ratio; IM, intramuscular;

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NMA, network meta-analysis; OR, odds ratio; PSA, prostate-specific antigen; TU, testosterone undecanoate.

Delivery routes: pharmacokinetics decide the risk profile, not the efficacy

Because every approved testosterone product delivers the same molecule, the choice between them is a choice about the shape of the serum concentration curve and about route-specific hazards, not about anabolic potency. The peak-to-trough ratio across approved formulations spans nearly threefold, from 1.8 with the weekly subcutaneous enanthate autoinjector to 5.3 with short-acting intramuscular esters [38]. The proportion of treated men brought into the eugonadal range is remarkably similar — between 80% and 94% for every modern product [39–42] — so the differentiating factors are erythrocytosis risk, secondary exposure, injection-site and delivery-specific toxicity, and adherence.

Four route-specific hazards deserve explicit mention. Transdermal gels carry a boxed warning for secondary exposure and virilisation of women and children after paediatric cases were reported to the FDA [41]. Intramuscular testosterone undecanoate retains a boxed warning for pulmonary oil microembolism and anaphylaxis, with nine events reported in eight of 3,556 patients in the development programme, and is dispensed under a restricted programme requiring 30 minutes of post-injection observation [39]. The transdermal patch produces application-site reactions in 28% of users at the 4 mg dose [43]. Nasal gel has the highest peak-to-trough ratio of any product (4.7) but, because of its very short exposure pulses, appears not to suppress luteinising hormone into the subnormal range or to reduce sperm concentration at six months, which makes it the preferred option where fertility must be preserved [44,45]. Blood-pressure boxed warnings on the oral undecanoate products and on the subcutaneous autoinjector were removed in July 2025, although the underlying ambulatory blood-pressure increases of roughly 1.7 to 4.9 mmHg systolic remain in the labels [40,46,47].

The 17α-alkylated oral androgens — methyltestosterone and oxymetholone — are a separate category and should not be conflated with modern oral testosterone undecanoate, which is absorbed through the lymphatics and is not alkylated. Alkylation confers oral bioavailability at the price of hepatotoxicity: oxandrolone carries a boxed warning for peliosis hepatis, liver-cell tumours and marked lipid changes, and acute cholestasis occurs in approximately 1% of users of alkylated androgens [48]. Table 6 sets out the comparative pharmacology, and Figure 4 displays it graphically.

Route / product	Dose and interval	C-avg (ng/dL)	Peak: trough	% eugonadal	Principal route-specific hazard
Gel 1% (AndroGel)	50 mg daily, titrate to 100 mg	555±225	2.2–2.4	87%	Boxed warning: secondary exposure and virilisation of children
Gel 1.62%	40.5 mg daily (20.25–81)	561±259	—	82% at day 112	Same boxed warning for secondary exposure
Patch (Androderm)	4 mg nightly	C-max 696±158, T-max 8 h	—	97%	Application-site reactions in 28% at 4 mg
Buccal (Striant)	30 mg twice daily	520±205	3.3	87%	Gum irritation 9.2%; discontinued in the United States
IM cypionate	50–400 mg every 2–4 weeks	peak 1,112±297 at 200 mg q2wk	2.0–5.3	n.a.	Supraphysiological peaks; largest haematocrit rise
IM enanthate	50–400 mg every 2–4 weeks	C-max >1,200 for all regimens	2.0–5.3	n.a.	Supraphysiological peaks; peliosis hepatis with prolonged high dose
IM undecanoate (Aveed)	750 mg at 0 and 4 weeks, then every 10 weeks	495±142	2.6–2.8	94%	Boxed warning: pulmonary oil microembolism and anaphylaxis; 30-minute observation required
SC enanthate (Xyosted)	75 mg weekly	553±127	1.8	90%; no patient with C-max >1,500	Flattest profile; blood-pressure warning downgraded July 2025
Pellets (Testopel)	150–450 mg every 3–6 months	638±124 at 900 mg	—	n.a.	Extrusion 2.58% and infection 0.41% across 1.2 million procedures

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Route / product	Dose and interval	C-avg (ng/dL)	Peak: trough	% eugonadal	Principal route-specific hazard
Oral TU (Jatenzo)	237 mg twice daily with food	403±128	~4	87%	Ambulatory blood pressure +4.9/2.5 mmHg; not 17α-alkylated
Oral TU (Tlando)	225 mg twice daily with food	476	—	80% (72–88)	Ambulatory systolic blood pressure +4.3 mmHg
Oral TU (Kyzatrex)	200 mg twice daily with food	393±114	—	88% (82–93)	Smallest blood-pressure signal (+1.7 mmHg systolic)
Nasal gel (Natesto)	11 mg three times daily	421±116	4.7	90%	Preserves luteinising hormone and sperm concentration at 6 months
17α-alkylated orals	Methyltestosterone 10–50 mg/day; oxandrolone 2.5–20 mg/day	—	—	—	Boxed warning for peliosis hepatis and liver-cell tumours; cholestasis ~1%

Table 6: Comparative pharmacology of testosterone delivery systems. C-avg, average steady-state serum concentration; IM, intramuscular; SC, subcutaneous; TU, testosterone undecanoate; n.a., not available in the retrieved label. Values are from United States prescribing information and a comparative pharmacokinetic review [38].

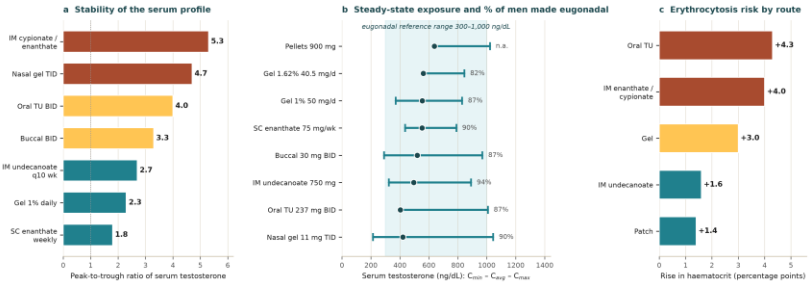

Figure 4: Testosterone delivery routes differ in kinetics and hazard, not in anabolic potency. (a) Peak-to-trough ratio of serum testosterone spans threefold across approved products; the weekly subcutaneous autoinjector gives the flattest profile and short-acting intramuscular esters the most volatile one. Teal denotes a ratio at or below 3.0, amber 3.0 to 4.5, and rust above 4.5. (b) Steady-state exposure: the marker is the average concentration and the bar spans trough to peak, against the shaded eugonadal reference range; the percentage to the right of each bar is the proportion of treated men brought into that range, which is between 80% and 94% for every modern product. (c) Mean rise in haematocrit by route from a network meta-analysis of 29 randomised trials in 3,393 men.

Monitoring is therefore route-aware but principle-identical. The Endocrine Society recommends measuring serum testosterone at three to six months after initiation — timed to the formulation — and annually thereafter, targeting the mid-normal range; measuring haematocrit at baseline, at three to six months and annually, stopping therapy if it exceeds 54% and evaluating the patient for hypoxia and sleep apnoea before restarting at a reduced dose; and performing prostate-specific antigen measurement and digital rectal examination before initiation and again three to twelve months afterwards in men aged 55 to 69 [10]. Notably, no FDA label contains a numeric haematocrit threshold, so this guidance is guideline-derived rather than regulatory.

Selective Androgen Receptor Modulators: A Class Defined By Its Failures

SARMs were designed to dissociate the anabolic effects of androgens on muscle and bone from their androgenic effects on prostate, skin and hair. Pharmacologically, the concept worked. Therapeutically, it has failed at every attempt.

Enobosarm (GTx-024) produced a dose-dependent increase in total lean body mass ($P<0.001$) and an

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improvement in stair-climb power (P=0.013) in a 12-week phase 2 trial of 120 healthy elderly men and postmenopausal women, with a gain of approximately 1.3 kg at the 3 mg dose [49]. In cancer cachexia it increased lean body mass by 1.5 kg (P=0.0012) and stair-climb power by 18.0% at 1 mg and 21.7% at 3 mg, against 4.8% for placebo [50]. On the strength of these results, two identical phase 3 trials — POWER 1 and POWER 2 — were conducted in patients with non-small-cell lung cancer receiving chemotherapy, using co-primary responder endpoints for lean body mass and stair-climb power [51]. Neither trial met its co-primary endpoints. Lean-mass responder analyses gave p=0.036 in POWER 1 and p=0.113 in POWER 2; the stair-climb power endpoint, the functional co-primary, gave p=0.315 and p=0.289 [12]. A physical-function signal that had been significant in two consecutive phase 2 trials evaporated entirely on replication at scale.

MK-0773 is the cleanest illustration of the class problem because it was tested specifically in sarcopenia. In 170 sarcopenic older women treated for six months, lean body mass rose by 1.00 kg (0.59–1.14, P<0.001) — a highly significant, unambiguous anabolic effect — while leg-press strength did not change (p=0.269) and the Short Physical Performance Battery moved by 0.15 points (−0.38 to 0.68), a difference indistinguishable from zero and far below any plausible minimal important difference [13]. The programme was discontinued. GSK2881078 reproduced the same pattern: dose-dependent lean-mass gain with high-density lipoprotein reduction and transient alanine aminotransferase elevations in healthy older volunteers [52], and increased lean mass without corresponding functional benefit in a phase 2a trial in chronic obstructive pulmonary disease with muscle weakness [53].

Agent	Trial and design	Population	Mass outcome	Function outcome	Programme status
Enobosarm (GTx-024)	Phase 2, n=120, 12 wk [49]	Healthy elderly men and postmenopausal women	Dose-dependent LBM increase, P<0.001; ~+1.3 kg at 3 mg	Stair-climb power P=0.013	Advanced to phase 3
Enobosarm	Phase 2 in cachexia, 12 wk [50]	Cancer cachexia	LBM +1.5 kg at 1 mg, P=0.0012	Stair-climb power +18.0% (1 mg) / +21.7% (3 mg) vs +4.8% placebo	Advanced to phase 3
Enobosarm	POWER 1 and POWER 2, two identical phase 3 RCTs [12,51]	NSCLC on chemotherapy	LBM responder p=0.036 / p=0.113	Stair-climb power responder p=0.315 / p=0.289	Both co-primary endpoints missed; not approved
MK-0773	Phase 2, n=170, 6 mo [13]	Sarcopenic older women	LBM +1.00 kg (0.59–1.14), P<0.001	Leg press p=0.269; SPPB 0.15 (−0.38 to 0.68)	Discontinued
GSK2881078	Phase 1 dose-finding [52]	Healthy older men and postmenopausal women	Dose-dependent lean-mass gain	Not assessed as a primary endpoint; HDL reduction and transient ALT rises	Did not proceed to phase 3 in sarcopenia
GSK2881078	Phase 2a [53]	COPD with muscle weakness	Increased lean mass	No corresponding functional benefit	Discontinued
RAD140 (testolone)	No completed sarcopenia RCT identified [18]	—	n.a.	n.a.	Never developed for sarcopenia; appears in drug-induced liver injury reports

Table 7: Selective androgen receptor modulators tested for muscle wasting. ALT, alanine aminotransferase; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; LBM, lean body mass; NSCLC, non-small-cell lung cancer; SPPB, Short Physical Performance Battery. Every agent that reached a functional endpoint failed it.

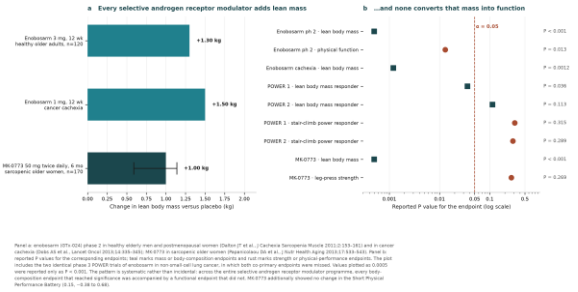

Figure 5: Selective androgen receptor modulators separate mass from function. (a) Every agent tested produced a statistically robust increase in lean mass. (b) The same trials, plotted by the P value of their functional endpoint: only the two small phase 2 studies of enobosarm crossed the conventional threshold, and both signals disappeared on replication in the phase 3 POWER programme. Teal marks mass endpoints and rust marks functional endpoints; the dashed line is P=0.05.

Safety and legal status complete the picture. No SARM is approved for any indication in any major jurisdiction. A systematic review of case reports identified fifteen published cases of SARM-associated drug-induced liver injury and a mean 7.1% rate of alanine aminotransferase elevation across clinical trials [18], and pharmacovigilance analysis identified twenty consumer adverse-event reports since 2020 [54]. The FDA has issued warning letters to manufacturers marketing SARM-containing products as dietary supplements [55], and SARMs have been prohibited at all times under class S1.2 of the World Anti-Doping Agency Prohibited List since 2008 [17,56]. A patient who obtains a SARM outside a trial is taking an unapproved, unmonitored, potentially hepatotoxic compound of uncertain identity and dose, in pursuit of a benefit that three phase 2 and two phase 3 trials have failed to demonstrate.

Legacy Anabolic-Androgenic Steroids: Nandrolone, Oxandrolone And Oral Testosterone Undecanoate

Nandrolone decanoate is the agent most often credited with the highest “effectiveness” in informal rankings. The evidence supports a real and unusually consistent effect on tissue mass, and nothing more. A 2026 systematic review and meta-analysis of twenty randomised trials found a lean-soft-tissue gain of 1.59 kg (95% CI 1.06–2.13) with no heterogeneity at all (I^2=0%) — a rare finding in this literature and strong evidence that the anabolic effect is genuine and reproducible. In the same analysis, fat mass was unchanged (SMD −0.04, p=0.65) and handgrip strength did not reach significance (SMD 0.39, p=0.10) [57]. The largest single-trial effects come from dialysis populations, where nandrolone 100 mg weekly for six months raised lean body mass by 4.5±2.3 kg against 1.9±1.6 kg (P=0.005) [58], and a factorial trial found nandrolone increased lean body mass by 3.1±2.2 kg (P<0.001) while resistance exercise alone did not [59].

The decisive negative experiment is the disuse model. Thirty healthy men underwent seven days of one-leg cast immobilisation after a single 200 mg intramuscular dose of nandrolone decanoate or control. Quadriceps cross-sectional area fell by 5.5±0.8% in controls and 5.8±0.7% with nandrolone (time × treatment P=0.59), and one-repetition-maximum leg extension fell by 5.6% and 6.9% respectively (P=0.55) [60]. An agent that adds mass in a stable state offers no protection whatever against the catabolic stimulus — immobility — that drives most acute muscle loss in older patients.

Oxandrolone occupies a different position again: it was the archetypal anabolic prescription drug for

catabolic states [61], and it is now unavailable in the United States. Approval of Oxandrin and four generic applications was withdrawn effective 28 June 2023 [11,62]. The most recent meta-analysis in burn injury, covering fourteen randomised trials and 2,822 patients, found a lean-mass standardised mean difference of 1.30 (−0.47 to 3.24) with heterogeneity of 95% or above, a reduction in the number of surgeries (SMD −1.25, −2.45 to −0.04, p=0.04, I^2=97.2%), no mortality benefit (RR 1.04, 0.47–2.32, p=0.913), no significant reduction in infection (RR 0.83, 0.67–1.02), and a near-fourfold increase in transaminase elevation in adults (19% versus 5%, p=0.002) [63]. An earlier synthesis found mortality RR 0.72 (0.47–1.08) and progressive liver dysfunction RR 1.04 (0.59–1.85) [64], and a retrospective cohort found transaminitis in 28 of 66 treated burn patients (42%) [65].

Oral testosterone undecanoate in a self-emulsifying drug delivery system is the one genuinely new oral androgen. It restores eugonadal average concentrations in 87% of treated hypogonadal men, with a plasma average of 403±128 ng/dL [42,66], and 80–88% across the three approved products, without clinically significant hepatotoxicity, although 7.2% of patients require escalation of antihypertensive therapy [47]. Its ambulatory blood-pressure effect is +4.9/2.5 mmHg, rising to +5.4/3.2 mmHg in hypertensive patients, and its boxed warning for blood-pressure increases was removed in July 2025 [46]. It is approved for hypogonadism. It has never been tested in sarcopenia. (Table 8 and Figure 6) summarise this domain.

Agent	Evidence	Mass effect	Functional effect	Safety and status
Nandrolone decanoate	SR/MA of 20 RCTs [57]	Lean soft tissue +1.59 kg (1.06–2.13), I^2=0%	Handgrip SMD 0.39, p=0.10 (NS); knee extension k=1, p=0.99	Schedule III; suppresses the hypothalamic–pituitary–gonadal axis
Nandrolone in dialysis	RCT, n=29, 6 mo [58]	LBM +4.5±2.3 vs +1.9±1.6 kg, P=0.005	Not the primary endpoint	Largest reported mass effect in any population
Nandrolone ± exercise	2×2 factorial RCT, n=79, 12 wk [59]	LBM +3.1±2.2 kg, P<0.001	Exercise alone produced no lean-mass gain	Quadriceps cross-sectional area increased with both
Nandrolone in disuse	RCT, n=30, 7-day immobilisation [60]	Quadriceps CSA −5.5% control vs −5.8% nandrolone, P=0.59	1RM −5.6% vs −6.9%, P=0.55	No protection against disuse atrophy
Oxandrolone in burns	SR/MA, 14 RCTs, n=2,822 [63]	Lean mass SMD 1.30 (−0.47 to 3.24), I^2≥95%	Surgeries SMD −1.25 (−2.45 to −0.04), p=0.04	Transaminase elevation 19% vs 5%, p=0.002; mortality RR 1.04 (0.47–2.32)
Oxandrolone — regulatory	Federal Register [11]	—	—	United States approval withdrawn effective 28 June 2023
Oral TU (SEDDS)	Pivotal studies and class review [42,47]	Not studied as a mass endpoint in sarcopenia	Not studied	80–88% eugonadal; ABPM +4.9/2.5 mmHg; approved only for hypogonadism

Table 8: Legacy anabolic-androgenic steroids and oral testosterone undecanoate. ABPM, ambulatory blood pressure monitoring; CSA, cross-sectional area; LBM, lean body mass; NS, not significant; 1RM, one repetition maximum; SEDDS, self-emulsifying drug delivery system; SMD, standardised mean difference; TU, testosterone undecanoate.

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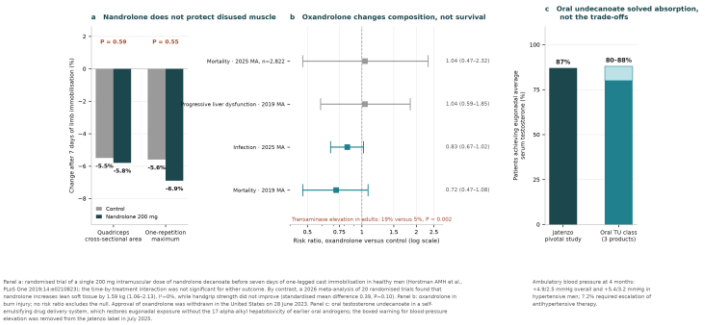

Figure 6: Legacy androgens: reproducible mass, absent function, real toxicity. (a) A single 200 mg dose of nandrolone decanoate did not attenuate the loss of quadriceps cross-sectional area or leg-extension strength over seven days of cast immobilisation. (b) Pooled risk ratios from randomised trials of oxandrolone in burn injury: no mortality or infection benefit, and a marked excess of transaminase elevation. (c) Proportion of hypogonadal men achieving eugonadal average testosterone concentrations with each approved oral testosterone undecanoate product; none has been studied in sarcopenia.

Myostatin Pathway Inhibitors, Growth Hormone, Ghrelin Agonists And The Incretin Era

Blocking the myostatin–activin signalling axis produces the largest pharmacological increases in human muscle mass ever recorded, and the clearest demonstration that muscle mass is not the same thing as muscle function. Bimagrumab, a monoclonal antibody against the activin type II receptor, increased thigh muscle volume by 7.72±5.31% versus 0.42±5.14% (P<0.001) in a 40-participant proof-of-concept trial, with encouraging gait-speed and 6-minute walk signals in the slow-walking subgroup [67]. The definitive trial randomised 180 community-dwelling adults aged 70 and over with sarcopenia, all of whom received diet and exercise. Lean body mass rose by 7% with bimagrumab versus 1% with standard of care, a difference of 6 percentage points (4–7, P<0.001). The Short Physical Performance Battery improved by 1.34 points (0.90–1.77) with bimagrumab and 1.03 (0.53–1.52) without it (P=.13); 6-minute walk distance rose 24.60 m versus 14.30 m (P=.16); gait speed rose 0.14 versus 0.11 m/s (P=.16) [14]. A meta-analysis across trials confirms thigh muscle volume +5.29% (4.08–6.50) and fat-free mass +1.90 kg (1.57–2.23) with no strength or physical-performance benefit [15]. Landogrozumab, an anti-myostatin antibody, increased appendicular lean body mass by 0.43 kg (0.192–0.660, p<0.0001) in 201 older fallers, at the cost of injection-site reactions in 30% versus 9% [68], and missed its primary objective in a hip-arthroplasty trial [69].

Growth hormone in healthy elderly people follows the same rule. Across eighteen studies, it reduced fat mass by 2.1 kg (−2.8 to −1.35) and increased lean body mass by 2.1 kg (1.3–2.9, P<0.001) without changing body weight, while increasing rates of oedema, arthralgia, carpal tunnel syndrome, gynaecomastia and impaired fasting glucose or diabetes [70]. No functional benefit was demonstrated. Anamorelin, an orally active ghrelin receptor agonist, increased lean body mass by a median of 0.99 kg (0.61–1.36) in ROMANA 1 and 0.65 kg (0.38–0.91) in ROMANA 2 against losses in both placebo arms (p<0.0001), while handgrip strength — the co-primary endpoint — showed no difference in either trial (p=0.15 and p=0.65) [71].

The most consequential recent development is not a sarcopenia treatment at all. Incretin-based weight-loss therapy has created a very large population losing lean mass rapidly. In the STEP 1 dual-energy X-ray

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absorptiometry substudy, semaglutide 2.4 mg reduced body weight by about 15% and lean mass by 9.7%, with roughly 34% of the weight lost being lean tissue, even though the lean proportion of body mass rose by 3.0 percentage points [72,73]. This has redirected the entire myostatin field. In the BELIEVE trial, the composition of weight lost at 48 weeks was 71.5% fat with semaglutide alone, 92.9% fat with semaglutide plus bimagrumab and 100% fat with bimagrumab alone; at 72 weeks, lean mass fell 7.4% with semaglutide, fell 2.9% with the combination and rose 2.5% with bimagrumab alone [74]. In EMBRAZE, adding apitegromab to tirzepatide shifted the composition of weight loss from 70% fat and 30% lean to 85% fat and 15% lean, a 54.9% relative reduction in lean-mass loss (p=0.001) [75]. Whether preserved lean mass in this setting translates into preserved function remains unproven and is the subject of active clinical guidance [76].

Agent and mechanism	Trial	Mass outcome	Function outcome	Verdict
Bimagrumab — anti-ActRII antibody	Phase 2, n=40, 16 wk [67]	Thigh muscle volume +7.72±5.31% vs +0.42±5.14%, P<0.001	Gait +0.15 m/s (P=.009) and 6MWD +82 m (P=.022) in slow walkers only	Signal in a subgroup
Bimagrumab	Phase 2b, n=180, 24 wk, all on diet and exercise [14]	Lean body mass +7% vs +1%, difference 6% (4–7), P<0.001	SPPB 1.34 vs 1.03, P=.13; 6MWD 24.60 vs 14.30 m, P=.16; gait 0.14 vs 0.11 m/s, P=.16	Mass yes, function no
Bimagrumab	SR/MA of RCTs [15]	TMV +5.29% (4.08–6.50); FFM +1.90 kg (1.57–2.23)	No strength or physical-performance benefit	Class conclusion
Landogrozumab — anti-myostatin	Phase 2, n=201, 24 wk [68]	Appendicular LBM +0.43 kg (0.192–0.660), p<0.0001	Not translated into the primary functional gain	Injection-site reactions 30% vs 9%
Landogrozumab	Phase 2, elective hip arthroplasty [69]	—	Primary objective not met	Discontinued
Growth hormone	SR/MA, 18 studies, mean 27 wk [70]	LBM +2.1 kg (1.3–2.9), P<0.001; fat −2.1 kg (−2.8 to −1.35)	No functional benefit demonstrated	Oedema, arthralgia, carpal tunnel syndrome, gynaecomastia, diabetes
Anamorelin — ghrelin agonist	ROMANA 1 and 2, phase 3, 12 wk [71]	LBM +0.99 kg (0.61–1.36) and +0.65 kg (0.38–0.91), p<0.0001	Handgrip no difference, p=0.15 and p=0.65	Mass yes, function no
Semaglutide 2.4 mg	STEP 1 DXA substudy, n=140, 68 wk [72,73]	Weight −15%; lean mass −9.7%; ~34% of weight lost was lean tissue	Not assessed	Creates the problem the myostatin class may solve
Bimagrumab + semaglutide	BELIEVE, phase 2b, n=507, 72 wk [74]	Fat fraction of weight lost at 48 wk: 71.5% semaglutide, 92.9% combination, 100% bimagrumab alone; lean mass at 72 wk −7.4% / −2.9% / +2.5%	Not the primary endpoint	Adverse-event discontinuation 14.0–21.4%
Apitegromab + tirzepatide	EMBRAZE, phase 2, 24 wk [75]	Composition of weight lost 85% fat / 15% lean vs 70/30; 54.9% relative reduction in lean-mass loss, p=0.001	Not assessed	Most promising near-term indication for the class

Table 9: Non-androgenic pharmacology and the incretin era. ActRII, activin type II receptor; DXA, dual-energy X-ray absorptiometry; FFM, fat-free mass; LBM, lean body mass; 6MWD, six-minute walk distance; SPPB, Short Physical Performance Battery; TMV, thigh muscle volume.

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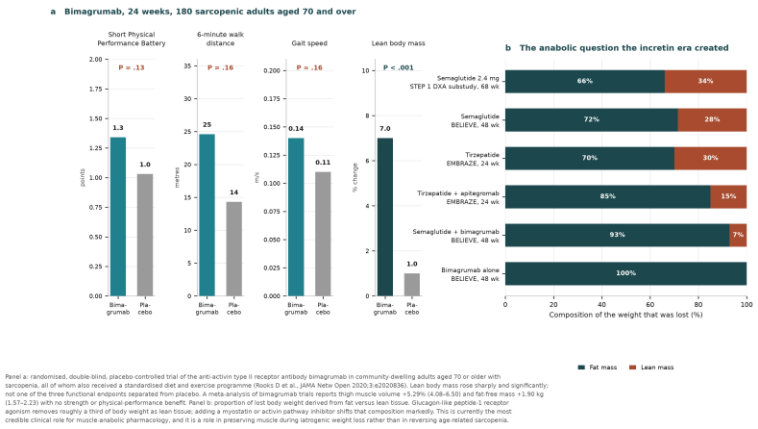


Figure 7: Myostatin blockade and the incretin problem. (a) In the definitive bimagrumab trial in 180 sarcopenic older adults, the lean-mass difference was unambiguous (P<0.001) while all three functional endpoints — Short Physical Performance Battery, six-minute walk distance and gait speed — failed to separate from optimised standard of care. (b) Composition of weight lost during incretin-based therapy, with and without a myostatin-pathway agent: the addition of bimagrumab or apitegromab shifts the loss decisively towards fat, which is the most defensible near-term application of the class.

Nutritional Adjuncts: Small, Real And Dependent On Training

Nutritional interventions produce effects an order of magnitude smaller than anabolic drugs on muscle mass, and yet they occupy a higher tier in this framework, because their effects are consistent, safe, inexpensive and — when combined with training — accompanied by measurable strength gains. Creatine monohydrate taken during resistance training in older adults increases lean tissue mass by 1.37 kg (0.97–1.76, p<0.00001) and improves chest press (SMD 0.35, 0.16–0.53) and leg press (SMD 0.24, 0.05–0.43) [77]. Protein supplementation added to resistance training increases fat-free mass by 0.30 kg (0.09–0.52) and one-repetition-maximum strength by 2.49 kg (0.64–4.33), with a meta-regression showing that benefit plateaus at a total intake of 1.62 g/kg/day and that the effect attenuates with advancing age [78]. Leucine-rich supplements increase lean body mass by 0.99 kg (0.43–1.55, p=0.0005) without a strength effect [79].

Two widely marketed adjuncts do not survive scrutiny. β-hydroxy-β-methylbutyrate improves muscle mass modestly when given alone (SMD 0.352, 0.11–0.594, p=0.004) [80], but a 2026 synthesis of thirteen randomised trials found that adding it to resistance training contributes essentially nothing: muscle mass SMD 0.05 and strength SMD 0.04 [81]. Vitamin D, outside of correcting documented deficiency, does not improve musculoskeletal outcomes: across 81 trials and 53,537 participants, total fracture risk ratio was 1.00 (0.93–1.07), hip fracture 1.11 (0.97–1.26) and falls 0.97 (0.93–1.02) [82], and grip strength did not improve (+0.2 kg, −0.25 to 0.7) [83]. A dose-stratified network meta-analysis of 35 trials in 58,937 participants did find a fall reduction confined to the 800–1,000 IU/day range (RR 0.85, 0.74–0.95), with higher doses performing worse [84].

Intervention	Synthesis	Mass effect	Strength or function effect	Practical conclusion
Creatine monohydrate + resistance training	SR/MA, 22 studies, n=721 [77]	Lean tissue +1.37 kg (0.97–1.76), p<0.00001	Chest press SMD 0.35 (0.16–0.53); leg press SMD 0.24 (0.05–0.43)	The only supplement that reliably improves both mass and strength

Intervention	Synthesis	Mass effect	Strength or function effect	Practical conclusion
Protein supplementation + resistance training	SR/MA + meta-regression, 49 studies, n=1,863 [78]	Fat-free mass +0.30 kg (0.09–0.52)	1RM +2.49 kg (0.64–4.33); benefit plateaus at 1.62 g/kg/day	Adequate intake matters more than supplementation
Leucine-rich supplements	SR/MA [79]	Lean body mass +0.99 kg (0.43–1.55), p=0.0005	No strength effect	Reasonable adjunct where protein intake cannot be raised by food
HMB alone	SR/MA, 7 RCTs, n=287 [80]	Muscle mass SMD 0.352 (0.11–0.594), p=0.004	Not established	Modest signal in the absence of training
HMB added to resistance training	SR/MA, 13 RCTs, n=561 [81]	Muscle mass SMD 0.05	Strength SMD 0.04	No additional benefit over training alone
Vitamin D — musculoskeletal outcomes	SR/MA + trial sequential analysis, 81 RCTs, n=53,537 [82]	BMD differences −0.16% to +0.76%	Total fracture RR 1.00 (0.93–1.07); hip fracture 1.11 (0.97–1.26); falls 0.97 (0.93–1.02)	No benefit beyond correcting documented deficiency
Vitamin D — muscle strength	SR/MA, 15 studies, n=2,866 [83]	—	Grip +0.2 kg (−0.25 to 0.7), not significant	No strength benefit
Vitamin D — falls by dose	NMA, 35 RCTs, n=58,937 [84]	—	800–1,000 IU/day RR 0.85 (0.74–0.95); >1,000 IU/day worse	Dose matters; more is not better

Table 10: Nutritional adjuncts. BMD, bone mineral density; HMB, β-hydroxy-β-methylbutyrate; NMA, network meta-analysis; 1RM, one repetition maximum; RR, risk ratio; SMD, standardised mean difference.

Exercise: The Reference Standard Against Which Every Drug Must Be Judged

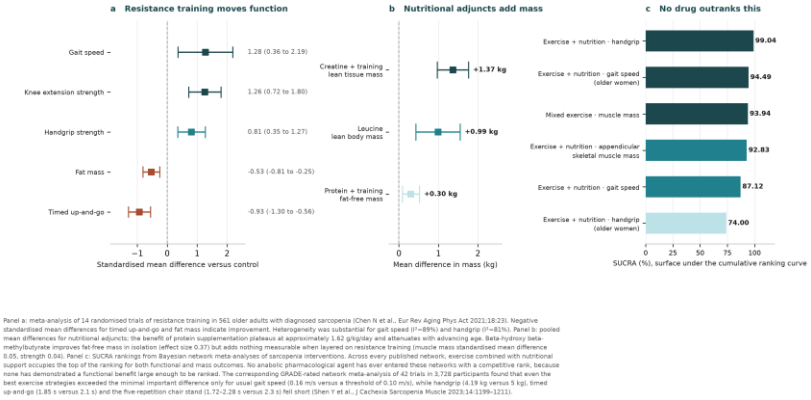
Resistance training is the only intervention in this review with consistent benefit across all three outcome families. In fourteen randomised trials of 561 older adults with sarcopenia, resistance training improved knee-extension strength (SMD 1.26, 0.72–1.80, I^2=67%), gait speed (SMD 1.28, 0.36–2.19, I^2=89%), handgrip strength (SMD 0.81, 0.35–1.27, I^2=81%), timed-up-and-go (SMD −0.93, −1.30 to −0.56) and fat mass (SMD −0.53, −0.81 to −0.25, I^2=0%) — while appendicular skeletal mass, skeletal muscle mass and leg lean mass all failed to reach significance [85]. This is the mirror image of the drug literature: function improves and mass does not.

The heterogeneity in those pooled estimates is high, and honesty requires stating the counter-evidence. A GRADE-rated network meta-analysis of 42 randomised trials in 3,728 participants found that although quality of life improved substantially (SMD 0.68–1.11, high to moderate certainty), most functional gains fell short of accepted minimal important differences: handgrip improved by 4.19 kg against a threshold of 5 kg, timed-up-and-go by 1.85 s against 2.1 s, and the five-times chair-stand test by 1.72–2.28 s against 2.3 s. Only gait speed exceeded its threshold, improving by 0.16 m/s against 0.10 m/s [86]. A 2025 synthesis of 24 trials reached the same conclusion [87]. Exercise is not a cure; it is simply the only intervention whose benefits are consistently in the right direction, on the right outcomes, at acceptable cost and risk.

Network meta-analyses converge on the same ranking. Mixed exercise ranks highest for muscle mass (SUCRA 93.94%) across 46 trials and 3,649 participants [88]. A Bayesian network meta-analysis of 35 trials in 2,331 participants found combined exercise plus nutrition ranked first for grip strength with a SUCRA of 99.04% (MD 3.69, 0.72–5.10) and 87.12% for gait speed [89]. In older women specifically, combined exercise and nutrition ranked first for gait speed (SUCRA 94.49%) and appendicular skeletal mass (92.83%) [90]. Resistance-band training with nutritional support produced the largest absolute effects retrieved in this review: grip +5.45 kg (3.58–7.33), gait +0.20 m/s (0.11–0.29), Short Physical Performance Battery +3.59 points (1.91–5.27) [91]. Crucially, in no network meta-analysis retrieved does any pharmacological agent occupy the top rank for any outcome.

Intervention	Synthesis	Outcome	Estimate (95% CI)	I^2 or SUCRA
Resistance training	SR/MA, 14 RCTs, n=561 [85]	Knee extension; gait speed; grip; TUG; fat mass	SMD 1.26 (0.72–1.80); 1.28 (0.36–2.19); 0.81 (0.35–1.27); −0.93 (−1.30 to −0.56); −0.53 (−0.81 to −0.25)	67%; 89%; 81%; —; 0%
Resistance training — mass	Same [85]	ASM; skeletal muscle mass; leg lean mass	All non-significant	—
Exercise — clinical relevance	NMA, 42 RCTs, n=3,728, GRADE-rated [86]	Quality of life; grip; gait; TUG; 5× chair stand	QoL SMD 0.68–1.11; grip 4.19 kg (MID 5); gait 0.16 m/s (MID 0.10); TUG 1.85 s (MID 2.1); 5CST 1.72–2.28 s (MID 2.3)	Only gait speed exceeds its MID
Resistance training dose–response	SR/MA, 12 studies, n=538 [92]	Grip; SPPB; skeletal muscle index	SMD 0.63 (0.43–0.83); 0.56 (0.18–0.94); 0.24 (−0.05 to 0.53) NS	32%; 53%; —
Resistance training in frailty	SR/MA [93]	Grip; lower-limb strength; gait; muscle mass	ES 0.51 (p=0.001); 0.93 (p<0.001); 0.75; 0.29 (p=0.002)	—
Mixed exercise	NMA, 46 RCTs, n=3,649 [88]	Muscle mass	Highest-ranked intervention	SUCRA 93.94%
Exercise + nutrition	Bayesian NMA, 35 RCTs, n=2,331 [89]	Grip; gait; ASMI	MD 3.69 kg (0.72–5.10); 0.11 m/s (0.03–0.17); 0.35 (0.19–0.49)	SUCRA 99.04%; 87.12%
Exercise + nutrition (older women)	NMA, 21 RCTs, n=1,215 [90]	Grip; gait; ASM	MD 1.95 (0.1–3.18); 0.11 (0.04–0.17); 0.21 (0.05–0.38)	SUCRA 74%; 94.49%; 92.83%
Resistance-band training + nutrition	NMA [91]	Grip; gait; SPPB; skeletal muscle index	MD 5.45 kg (3.58–7.33); 0.20 m/s (0.11–0.29); 3.59 (1.91–5.27); 0.95 kg/m² (0.16–1.74)	—

Table 11: Exercise and combined exercise–nutrition interventions. ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; 5CST, five-times chair-stand test; ES, effect size; MID, minimal important difference; NMA, network meta-analysis; NS, not significant; QoL, quality of life; SPPB, Short Physical Performance Battery; SUCRA, surface under the cumulative ranking curve; TUG, timed-up-and-go.



Panel a: meta-analysis of 14 randomised trials of resistance training in 561 older adults with diagnosed sarcopenia (Chen N et al., Eur Rev Aging Phys Act 2021;18:23). Negative standardised mean differences for timed up-and-go and fat mass indicate improvement. Heterogeneity was substantial for gait speed (I^2=89%) and handgrip (I^2=82%). Panel b: pooled mean differences for nutritional adjuncts; the benefit of protein supplementation plateaus at approximately 1.62 g/kg/day and attenuates with advancing age. Beta-hydroxy beta-methylbutyrate improves fat-free mass in isolation (effect size 0.37) but adds nothing measurable when layered on resistance training (muscle mass standardised mean difference 0.05, strength 0.04). Panel c: SUCRA rankings from Bayesian network meta-analyses of sarcopenia interventions. Across every published network, exercise combined with nutritional support occupies the top of the ranking for both functional and mass outcomes. No anabolic pharmacological agent has ever entered these networks with a competitive rank, because none has demonstrated a functional benefit large enough to be ranked. The corresponding GRADE-rated network meta-analysis of 42 trials in 3,728 participants found that even the best exercise strategies exceeded the minimal important difference only for usual gait speed (0.16 m/s versus a threshold of 0.10 m/s), while handgrip (4.19 kg versus 5 kg), timed up-and-go (1.85 s versus 2.1 s) and the five-repetition chair stand (1.72–2.28 s versus 2.3 s) fell short (Shen Y et al., J Cachexia Sarcopenia Muscle 2023;14:1199–1211).

Figure 8: Exercise is the reference standard. (a) Pooled standardised mean differences for resistance training in sarcopenic older adults: strength and performance outcomes improve consistently while mass outcomes do not — the exact inverse of the anabolic drug literature. (b) Nutritional adjuncts produce small but reproducible absolute gains, with creatine plus training the only supplement to improve both mass and strength. (c) Surface under the cumulative ranking curve values from network meta-analyses: exercise combined with nutrition ranks first for grip strength, gait speed and appendicular muscle mass, and no pharmacological agent occupies the top rank for any outcome.

The Central Finding: Dissociation Of Muscle Mass From Muscle Function

Read across the nine domains of this review, one pattern dominates everything else. Pharmacological agents that act on the androgen receptor or the myostatin–activin axis increase muscle mass with high reliability and improve physical function with essentially none; exercise-based interventions do the reverse. Figure 9 arranges every intervention in this review by the direction of its effect on mass, strength and performance, and the resulting matrix separates cleanly into two blocks.

The list of pharmacological agents that achieved a statistically robust mass effect and failed on function is now long enough to be diagnostic of the approach rather than of any individual molecule: MK-0773 (lean mass +1.00 kg, P<0.001; leg press p=0.269; SPPB 0.15) [13]; enobosarm in phase 3 (both co-primary endpoints missed) [12]; bimagrumab (thigh muscle volume +5.29%; no strength or performance benefit) [15]; anamorelin (lean mass +0.99 kg, p<0.0001; handgrip p=0.15) [71]; growth hormone (lean mass +2.1 kg; no functional benefit) [70]; nandrolone (lean soft tissue +1.59 kg, I^2=0%; handgrip p=0.10) [57]; and testosterone itself (lean mass +3.59 kg; pooled strength SMD 0.3, −0.0 to 0.6) [28,29].

There are at least four non-exclusive explanations, and they have different clinical implications. First, dual-energy X-ray absorptiometry lean mass includes water and non-contractile tissue, so a portion of the measured gain may not be functional muscle at all. Second, androgens and activin-receptor blockade may add myofibrillar protein without the neural adaptation — motor-unit recruitment, rate coding, coordination — that resistance training produces and that dominates early strength gains. Third, physical performance in older adults is constrained by pain, balance, cardiorespiratory fitness, fear of falling, cognition and polypharmacy, none of which an anabolic agent addresses. Fourth, the very definition problem described in Section 3 means many trials enrolled participants selected on low mass rather than low function, in whom a functional ceiling effect is unavoidable. The SDOC decision to exclude lean mass from the diagnostic criteria [4] is best read as the outcomes literature formally acknowledging this dissociation.

Intervention	Muscle mass	Muscle strength	Physical performance	Signature
Testosterone [27–29]	+3.59 kg (2.38–4.81), I^2=98%	SMD 0.3 (−0.0 to 0.6), not significant	6MWD responders 20.5% vs 12.6%, P=0.003 (pooled cohort only)	Mass, not function
Nandrolone [57,60]	+1.59 kg (1.06–2.13), I^2=0%	Handgrip SMD 0.39, p=0.10	No protection against disuse atrophy, P=0.59	Mass only
Oxandrolone [63]	SMD 1.30 (−0.47 to 3.24), I^2≥95%	Not established	Fewer surgeries; no mortality benefit	Mass only, with hepatic cost
Enobosarm [12]	Responder p=0.036 / 0.113	—	Stair-climb power p=0.315 / 0.289	Both co-primary endpoints missed
MK-0773 [13]	+1.00 kg (0.59–1.14), P<0.001	Leg press p=0.269	SPPB 0.15 (−0.38 to 0.68)	Mass only
Bimagrumab [14,15]	TMV +5.29% (4.08–6.50); FFM +1.90 kg	No benefit	SPPB P=.13; 6MWD P=.16; gait P=.16	Mass only
Landogrozumab [68]	+0.43 kg (0.192–0.660), p<0.0001	—	Primary objective not met in arthroplasty	Mass only
Growth hormone [70]	+2.1 kg (1.3–2.9), P<0.001	Not demonstrated	Not demonstrated	Mass only, with metabolic cost
Anamorelin [71]	+0.99 / +0.65 kg, p<0.0001	Handgrip p=0.15 / 0.65	—	Mass only
Creatine + training [77]	+1.37 kg (0.97–1.76)	Chest press SMD 0.35; leg press SMD 0.24	—	Mass and strength
Protein + training [78]	+0.30 kg (0.09–0.52)	1RM +2.49 kg (0.64–4.33)	—	Mass and strength
HMB + training [81]	SMD 0.05	SMD 0.04	—	Neither
Vitamin D [82,83]	—	Grip +0.2 kg, not significant	Fracture RR 1.00; falls RR 0.97	Neither
Resistance training [85]	ASM, SMM, leg lean mass all NS	Knee extension SMD 1.26; grip SMD 0.81	Gait SMD 1.28; TUG SMD −0.93	Function, not mass
Exercise + nutrition [89,90]	ASMI +0.35 (0.19–0.49)	Grip MD 3.69 kg, SUCRA 99.04%	Gait +0.11 m/s, SUCRA 87–94%	Function and mass

Table 12: The mass–function dissociation across all interventions reviewed. ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; FFM, fat-free mass; HMB, β-hydroxy-β-methylbutyrate; 6MWD, six-minute walk distance; NS, not significant; 1RM, one repetition maximum; SMM, skeletal muscle mass; SPPB, Short Physical Performance Battery; SUCRA, surface under the cumulative ranking curve; TMV, thigh muscle volume; TUG, timed-up-and-go.

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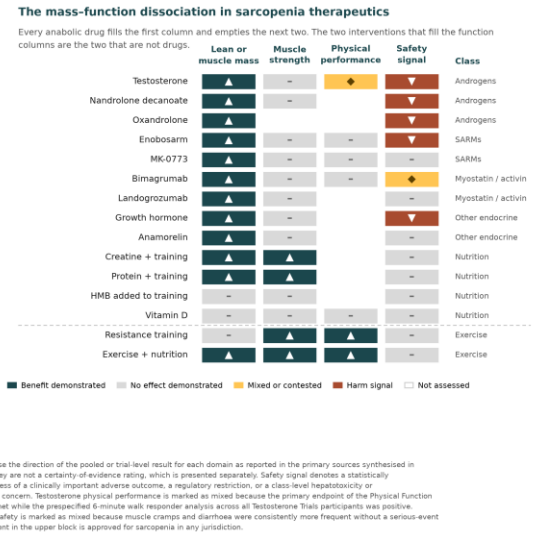

Figure 9: The signature of the field. Each row is an intervention and each column an outcome family; cells are coded by the direction and statistical status of the effect. Pharmacological agents cluster in the upper block, with robust mass effects and null function; exercise-based interventions cluster in the lower block, with the pattern reversed. No intervention in this review achieves large, certain benefit across all three outcome families.

Certainty of The Evidence

Certainty was appraised across four outcome families using GRADE domains: risk of bias in the contributing trials, inconsistency, indirectness, imprecision and publication bias [22]. The results, displayed in Figure 10 and tabulated in Table 13, are unflattering to the pharmacological field. No intervention reaches high certainty for a functional outcome. Several reach high or moderate certainty for a mass outcome, which is precisely the outcome the SDOC concluded should not define the disease.

Three sources of downgrading recur. Inconsistency is severe: I^2 is 98% for the pooled testosterone lean-mass effect [28], 95% or above for oxandrolone lean mass in burns [63], 89% for the gait effect of resistance training [85] and 99.7% for global prevalence estimates of anabolic-steroid use [16]. Indirectness is pervasive: much of the androgen evidence comes from hypogonadal men, dialysis patients, burn patients or cancer cachexia rather than from community-dwelling older adults with sarcopenia. Imprecision affects the SARM and myostatin literature, where individual trials are small and the confidence intervals around functional endpoints comfortably include both meaningful benefit and meaningful harm.

Intervention	Muscle mass	Muscle strength	Physical performance	Safety	Principal reason for downgrading
Testosterone (hypogonadal men)	Moderate	Low	Low	High	Inconsistency (I^2=98%) for mass; indirectness for sarcopenia; imprecision for strength
Testosterone (eugonadal older men)	Low	Very low	Very low	Moderate	Indirectness and sparse direct evidence
Nandrolone	Moderate	Very low	Very low	Low	Populations are dialysis and disuse, not sarcopenia; single-study strength estimates
Oxandrolone	Very low	Very low	Very low	Low	I^2≥95%; burn populations only; product withdrawn
Oral testosterone undecanoate	Not assessed	Not assessed	Not assessed	Moderate	No sarcopenia trial exists
Enobosarm	Low	Very low	Very low	Low	Phase 3 replication failure of a phase 2 signal
MK-0773	Moderate	Very low	Very low	Low	Single trial; functional endpoints null and imprecise

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Intervention	Muscle mass	Muscle strength	Physical performance	Safety	Principal reason for downgrading
Other SARMs	Very low	Very low	Very low	Very low	Phase 1–2 only; hepatotoxicity signal; no approved product
Bimagrumab	High	Low	Low	Moderate	Mass effect large and consistent; functional endpoints null across trials
Landogrozumab	Moderate	Very low	Very low	Moderate	Primary functional objective not met
Growth hormone	Moderate	Very low	Very low	Low	Consistent adverse-event excess; no functional data
Anamorelin	High	Low	Very low	Moderate	Cachexia population; handgrip co-primary null in both trials
Creatine + resistance training	High	Moderate	Low	High	Performance outcomes rarely measured
Protein + resistance training	High	Moderate	Moderate	High	Effect attenuates with age; plateau at 1.62 g/kg/day
Resistance training	Low	High	Moderate	High	Mass outcomes null; inconsistency (I^2=89%) for gait; several gains below the minimal important difference

Table 13: GRADE certainty of evidence by intervention and outcome family. Certainty was appraised against risk of bias, inconsistency, indirectness, imprecision and publication bias. Assessments were made by a single reviewer without formal adjudication and should be read as indicative rather than definitive.

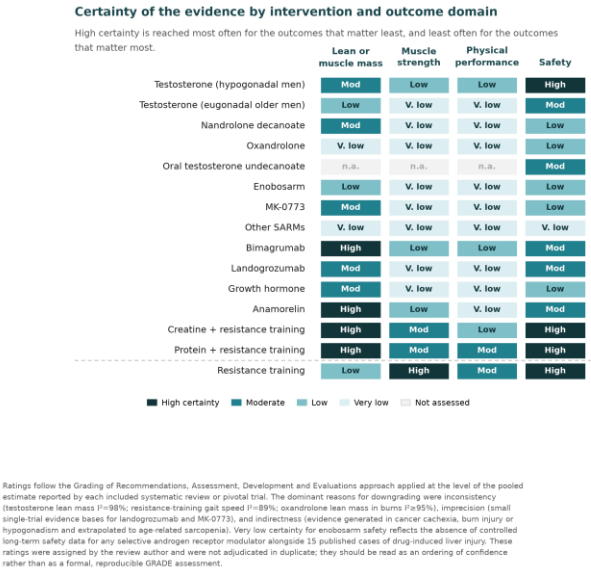

Figure 10: GRADE certainty of evidence across interventions and outcome families. Darker cells indicate greater certainty. High certainty is reached only for mass outcomes with bimagrumab, anamorelin, creatine and protein, and for the strength outcome with resistance training. No pharmacological agent reaches even moderate certainty for physical performance.

A Four-Tier Clinical Framework

The framework in Figure 11 orders interventions by the strength of the evidence for a functional benefit, not by the size of the effect on muscle mass. That ordering inverts most existing recommendations and is the practical conclusion of this review.

Tier 1 — offered to every patient who meets a case definition — is progressive resistance training two to three times weekly for at least twelve weeks, protein intake of 1.2 to 1.6 g/kg/day distributed across meals, correction of documented vitamin D deficiency, and review and deprescription of sarcopenia-

promoting drugs. This is the only tier supported by network meta-analytic evidence of consistent benefit across strength, performance and quality of life [85,86,89]. Tier 2 — adjuncts added when the Tier 1 response is inadequate at twelve weeks — comprises creatine monohydrate 3 to 5 g daily combined with training [77], leucine-enriched essential amino acids [79] and progression to multicomponent training that adds balance and aerobic work [88].

Tier 3 — endocrine correction — is testosterone replacement solely for symptomatic, biochemically confirmed hypogonadism on two morning measurements, never as an anabolic for eugonadal sarcopenia, with haematocrit, prostate-specific antigen and blood pressure monitored at three, six and twelve months, and with the expectation of body-composition change rather than functional change [10,94]. The Endocrine Society explicitly recommends against prescribing testosterone to improve physical function in older men with age-related decline alone, and the TRAVERSE fracture signal [35] reinforces that position. Tier 4 — investigational, inside a clinical trial only — contains SARMs, myostatin and activin pathway inhibitors, growth hormone and ghrelin agonists; within this tier, the most promising near-term indication is not sarcopenia at all but the preservation of lean mass during incretin-induced weight loss [74–76]. Below all four tiers sits a category with no acceptable role: non-prescribed anabolic-androgenic steroids, SARMs obtained outside a trial, oxandrolone, and supraphysiological androgen dosing in eugonadal older adults.

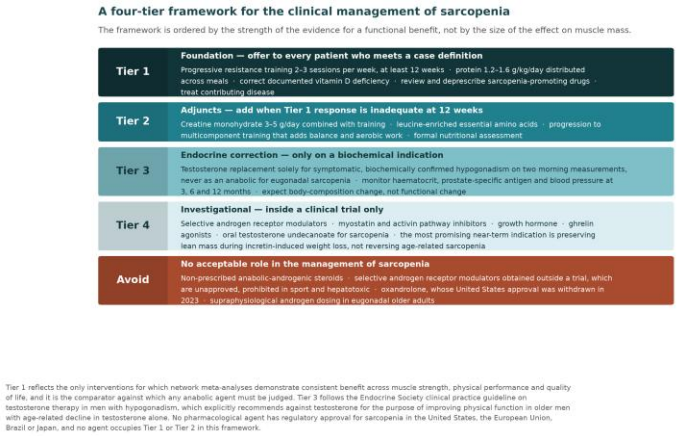

Figure 11: A four-tier framework for the clinical management of sarcopenia. Tiers are ordered by the strength of the evidence for a functional benefit rather than by the magnitude of the effect on muscle mass. No pharmacological agent occupies Tier 1 or Tier 2, and no agent has regulatory approval for sarcopenia in the United States, the European Union, Brazil or Japan.

Misuse, Harm And The Regulatory Landscape

Any discussion of anabolic treatment for sarcopenia takes place against a background of very substantial non-medical use. A meta-analysis of 187 studies estimated lifetime prevalence of anabolic-androgenic steroid use at 3.3% (2.8–3.8) globally — 6.4% in males and 1.6% in females — although with heterogeneity of 99.7%, which makes the point estimate close to uninterpretable and the underlying phenomenon undeniable [16]. The gap between that figure and the prevalence of sarcopenia itself — which varies from 9.9% to 40.4% depending on which definition is applied to the same cohort [95] — illustrates how much androgen exposure in the population is occurring outside any therapeutic rationale. Two prescribing

patterns sit in the same grey zone: subcutaneous testosterone pellets implanted at doses well above those studied in registration trials, reported in large uncontrolled clinic series [96], and newer oral testosterone undecanoate formulations whose approved indication remains hypogonadism rather than age-related functional decline [97].

The cardiac consequences are consistent and severe. In a cross-sectional study of 101 users and 71 controls, left ventricular ejection fraction was 49±7% versus 59±5% (P<0.001), with 11% of users below 40% and a further 36% between 41% and 49% [98]; a comparable study found 52±11% versus 63±8% (P<0.001), with current users at 49±10% and former users at 58±10% [99]. Meta-analysis confirms septal thickening (MD 1.33 mm, 0.8–1.89), reduced ejection fraction (MD −2.77%, −4.2 to −1.34) and impaired global longitudinal strain [100]. Prospective observation during a median 16-week cycle showed a 4.9 percentage point fall in three-dimensional ejection fraction (P<0.001) with recovery after cessation [101].

Reproductive suppression is near-universal and slow to reverse. In the prospective HAARLEM cohort, luteinising and follicle-stimulating hormone were almost completely suppressed during use; testosterone normalised in 90% of men by three months, but sperm concentration recovered only at 48 weeks [101]. Persistent hypogonadism lasting at least six months after cessation is now a recognised entity in men who used at least 150 mg weekly for at least six months [102]. In women, deepening of the voice is regarded as irreversible, and mild hirsutism occurs in approximately one in five women receiving 150 mg of testosterone enanthate every four weeks [103].

Regulatory control is uniform in direction and detail across jurisdictions. In the United States, anabolic steroids are Schedule III controlled substances [104]. In Brazil, they appear in Lista C5 of Portaria SVS/MS nº 344 of 12 May 1998 and require a special controlled prescription in duplicate [105], with the list expanded by RDC nº 98 of 2000 under Lei nº 9.965/2000 [106]. SARMs are prohibited in sport at all times under class S1.2 of the World Anti-Doping Agency Prohibited List [17]. Oxandrolone is no longer marketed in the United States [11]. Against this, no anabolic agent has been approved for sarcopenia anywhere, and the class-wide FDA labelling change of February 2025 relates to cardiovascular and blood-pressure language on testosterone products approved for hypogonadism, not to any new indication [34].

Discussion

This umbrella review set out to determine whether any anabolic treatment improves sarcopenia. The answer, on the evidence retrieved, is that anabolic agents improve the measurement of sarcopenia without improving the condition. The distinction is not semantic. A patient whose appendicular lean mass rises by a kilogram and whose gait speed, chair-stand time and fall risk are unchanged has not been treated; a surrogate has been treated.

Three implications follow for practice. First, the choice of endpoint is the choice of therapy. As long as trials are powered on dual-energy X-ray absorptiometry lean mass, drugs that add lean mass will keep succeeding in trials and failing in clinics. The SDOC position [4] and the GLIS consensus [9] both point towards strength- and performance-anchored endpoints, and future trials should adopt them and should power on the minimal important differences established by the exercise literature — approximately 5 kg for handgrip, 0.10 m/s for gait speed, 2.1 s for timed-up-and-go [86]. Second, testosterone should be

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reframed. It is a treatment for hypogonadism that has body-composition effects, not a treatment for sarcopenia that happens to require low testosterone. The fracture excess in TRAVERSE [35] makes that reframing urgent for exactly the population in whom sarcopenia is diagnosed. Third, the informal effectiveness rankings that circulate in clinical practice — nandrolone 35%, testosterone 30%, oxandrolone 25%, testosterone undecanoate 20% — have no retrievable evidentiary basis. No published synthesis generates them, and there is no common metric across those four agents from which they could be derived. They should be abandoned in favour of the pooled estimates in Tables 4, 6 and 8.

Three implications follow for research. The myostatin–activin class should be redirected. It has never demonstrated a functional benefit in sarcopenia across three trial programmes, but it demonstrably alters the composition of incretin-induced weight loss, shifting it from 70–71% fat to 85–100% fat [74,75]. That is a well-defined problem with a large and growing population, a measurable endpoint and a plausible mechanism, and it is a better use of the class than continued attempts at age-related muscle loss. Combination designs deserve testing: every successful functional result in this review involved training, and the Rooks trial gave bimagrumab on a background of diet and exercise [14] while the dialysis nandrolone factorial trial showed drug and exercise acting on different variables [59]. Finally, the enormous heterogeneity in this literature demands individual-participant-data synthesis rather than further aggregate pooling; an I^2 of 98% [28] means the pooled estimate describes no real patient.

These conclusions should be set against the mechanistic literature, which remains coherent even where the clinical literature is not. Testosterone and its derivatives increase satellite-cell number and myonuclear density, promote commitment of mesenchymal pluripotent cells towards the myogenic lineage and away from adipogenesis, and act through both genomic androgen-receptor signalling and non-genomic pathways involving IGF-1 and the suppression of myostatin [107,108]. The biology predicts hypertrophy, and hypertrophy is exactly what the trials deliver. What the biology does not predict, and what the trials do not deliver, is the neural and cardiorespiratory adaptation on which ambulation, chair rise and fall avoidance actually depend. Narrative and clinical reviews of anabolic therapy in older adults have reached broadly the same reading [109–113], as have syntheses of the wider intervention landscape [114,115].

Limitations

- This overview was not prospectively registered, and no protocol was published in advance.
- Screening, data extraction and GRADE assessment were performed by a single reviewer without duplicate independent assessment or formal adjudication of disagreements. Certainty ratings should therefore be read as indicative.
- No new quantitative pooling was performed; where syntheses disagreed, both are reported rather than reconciled.
- Heterogeneity in the underlying syntheses is extreme for several headline estimates (I^2=98% for testosterone lean mass, ≥95% for oxandrolone in burns, 89% for the gait effect of resistance training, 99.7% for global anabolic-steroid prevalence), which limits the interpretability of pooled point estimates.

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- Substantial indirectness affects the androgen evidence, which derives largely from hypogonadal, dialysis, burn and cancer-cachexia populations rather than from community-dwelling older adults meeting a sarcopenia case definition.
- Several agents could not be evaluated because no primary source with extractable results was retrievable: LY2452473, OPK-88004, RAD140, trevogrumab, and danazol, stanozolol and methandrostenolone in sarcopenia.
- A small number of values — principally from the BELIEVE and EMBRAZE programmes — are currently available only through a press release or a single publication and should be treated as provisional pending full peer review.
- Grey literature and trial registries were searched only opportunistically, so unpublished negative trials may be under-represented, which would bias this review towards over-estimating anabolic efficacy.

Conclusion

Sarcopenia doubles the risk of death, has a diagnostic code, three competing definitions and no approved drug. This umbrella review finds that every anabolic class developed for it — testosterone, selective androgen receptor modulators, legacy anabolic-androgenic steroids, myostatin and activin pathway inhibitors, growth hormone and ghrelin agonists — increases muscle mass and fails to improve physical function. Testosterone raises lean body mass by 3.59 kg with a pooled strength effect that crosses the null and a fracture hazard of 1.43. MK-0773 raises lean mass by a kilogram with a Short Physical Performance Battery change of 0.15 points. Bimagrumab raises thigh muscle volume by more than five per cent with no functional benefit at all. Oxandrolone has been withdrawn. Every selective androgen receptor modulator that reached a functional endpoint failed it.

The interventions that do improve function are unglamorous and available today. Progressive resistance training improves knee-extension strength, gait speed and timed-up-and-go in sarcopenic older adults, and combined exercise and nutrition ranks first in every network meta-analysis retrieved for this review. No drug ranks first for anything. The clinical implication is therefore not that anabolic pharmacology should be pursued more aggressively, but that it should be confined to biochemically justified endocrine replacement and to properly conducted clinical trials — with the most defensible near-term target being the preservation of lean mass during incretin-induced weight loss rather than the reversal of age-related muscle loss. Until a drug improves what a patient can do rather than what a scan can measure, exercise and adequate protein remain the treatment for sarcopenia.

Declarations

Ethics approval and consent to participate

Not applicable. This is a review of previously published aggregate data; no individual participant data, human subjects or animals were involved.

Consent for publication

Not applicable.

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Availability of data and materials

All data analysed in this review are contained within the published sources cited in the reference list. The full extraction table, including the source URL for every numeric value reported, is available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

All authors read and approved the final manuscript.

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Use of artificial intelligence

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