

RESEARCH MONOGRAPH . COMPOUND PROFILE

Anadrol

A 17-alpha-alkylated oral anabolic-androgenic steroid derived from dihydrotestosterone, developed at Syntex in the late 1950s for the treatment of anemias characterized by deficient red blood cell production, distinguished by potent erythropoietic stimulation, marked nitrogen retention, and significant hepatotoxic liability.

DOCUMENT	KDC-MN-1551
ISSUED	2026-05-15
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	17-alpha-alkylated anabolic-androgenic steroid; synthetic dihydrotestosterone derivative with potent erythropoietic and anabolic activity

ABSTRACT

Oxymetholone, marketed as Anadrol-50 (Syntex, later Unimed Pharmaceuticals, now Alaven Pharmaceutical) and Anapolon (Imperial Chemical Industries and generics), is a synthetic 17-alpha-alkylated derivative of dihydrotestosterone first described by Ringold et al. at Syntex in 1959 and introduced into clinical medicine in the early 1960s for the treatment of anemias, osteoporosis, and catabolic wasting states. The compound is the 2-hydroxymethylene analog of 17-alpha-methyl-dihydrotestosterone (mestanolone), bearing an unusual hydroxymethylene substituent at the C2 position that confers oral bioavailability through resistance to first-pass hepatic inactivation and that can be metabolically cleaved to yield mestanolone as an active metabolite. Oxymetholone is one of the most potent oral anabolic-androgenic steroids in clinical use, exhibiting a high ratio of anabolic to androgenic activity in classical levator ani and ventral prostate bioassays while paradoxically demonstrating low direct binding affinity for the androgen receptor in competitive displacement studies. The principal pharmacodynamic effects are stimulation of erythropoiesis through increased renal erythropoietin production (with urinary erythropoietin levels elevated up to fivefold at therapeutic doses), promotion of positive nitrogen balance and skeletal muscle protein synthesis, and a poorly characterized but clinically significant estrogenic activity that occurs despite the compound's structural inability to undergo aromatization, possibly through direct activation of estrogen receptor alpha. The compound received approval from the United States Food and Drug Administration for the treatment of anemias caused by deficient red blood cell production, including acquired

aplastic anemia, congenital aplastic anemia, myelofibrosis, and hypoplastic anemias due to the administration of myelotoxic drugs. In the mid-1970s, the FDA restricted the approved indication exclusively to anemias characterized by deficient erythropoiesis, withdrawing prior approvals for osteoporosis and general catabolic states. Clinical investigation has subsequently extended to HIV/AIDS-associated wasting (Hengge et al. 2003 Phase III trial demonstrating 3.0 to 3.5 kg weight gain over 16 weeks at 100 to 150 mg daily), antithrombin III deficiency, and pediatric growth failure, with varying degrees of success. The hepatotoxic liability of the 17-alpha-alkylated structure is the principal safety concern: cholestatic jaundice occurs in approximately 1 percent of treated patients, typically within 1 to 4 months of initiation; peliosis hepatis (blood-filled sinusoidal cysts) develops with prolonged administration and has resulted in fatal hepatic rupture and hemorrhage in case reports; and hepatocellular carcinoma and hepatic adenoma have been reported after 2 to 15 years of continuous use, predominantly in patients with Fanconi anemia and aplastic anemia receiving chronic androgen therapy. The compound is classified as a Schedule III controlled substance in the United States under the Controlled Substances Act and is subject to equivalent regulatory controls in most jurisdictions. This monograph reviews the chemistry, synthesis, and structure-activity relationships of oxymetholone; the androgen receptor, erythropoietic, and estrogenic pharmacology; the limited but clinically relevant pharmacokinetic record; the preclinical pharmacology in animal models of anemia and wasting; the clinical evidence base across anemia, HIV wasting, and ancillary indications; sourcing and quality verification for research applications; reconstitution and handling; stack interactions and combinations with other anabolic

and therapeutic agents; the adverse-event and safety signal including detailed hepatotoxicity characterization; and a comparative assessment of five alternative anabolic-androgenic agents (oxandrolone, nandrolone decanoate, stanozolol, testosterone enanthate, danazol) against oxymetholone on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Oxymetholone.

Marketed names: Anadrol-50 (Syntex, later Unimed Pharmaceuticals, later Alaven Pharmaceutical; United States), Anapolon (Imperial Chemical Industries; United Kingdom, Europe, and multiple international markets), Adroyd (Parke-Davis; United States, early marketing), Androlic (British Dispensary; Thailand and Southeast Asia), Oxitosona (Spain), Hemogenin (Brazil), Roboral (various international markets).

Development codes: None assigned in the conventional pharmaceutical development code format. The compound was developed under the Syntex steroid chemistry program in the late 1950s and was identified by its chemical name in the original Ringold et al. (1959) publication [1].

Chemical Abstracts Service registry number: 434-07-1.

International Union of Pure and Applied Chemistry name: (5 α ,17 β)-17-hydroxy-2-(hydroxymethylene)-17-methyl-androstan-3-one. The compound is the 2-hydroxymethylene derivative of mestanolone (17- α -methyl-5- α -androstan-17- β -ol-3-one), bearing a hydroxymethylene (=CHOH) substituent at the C2 position of the A ring.

United States Pharmacopeia name: Oxymetholone.

Drug Enforcement Administration Schedule: Schedule III controlled substance (United States, Controlled Substances Act).

1.2 Structural class and chemistry

Oxymetholone is a synthetic androstane steroid classified within the 17- α -alkylated anabolic-androgenic steroid family. It is a derivative of dihydrotestosterone (5- α -androstan-17- β -ol-3-one) bearing two structural modifications: a 17- α -methyl group that confers oral bioavailability by protecting the 17- β -hy-

droxyl from first-pass hepatic oxidation, and a 2-hydroxymethylene group (=CHOH at C2) that modifies the A-ring pharmacology and can be metabolically cleaved to yield mestanolone (17-alpha-methyl-DHT) as an active metabolite [2].

Molecular formula: C₂₁H₃₂O₃.

Molecular weight: 332.48 g/mol.

Exact mass: 332.2351 g/mol (monoisotopic).

Physical properties: White to creamy white crystalline powder. Practically insoluble in water; soluble in chloroform, dioxane, and dimethylformamide; sparingly soluble in ethanol and methanol. Melting point approximately 172 to 180 degrees Celsius.

Stereochemistry: The compound possesses the standard 5-alpha-androstane skeleton with trans A/B ring junction (5-alpha configuration). The 17-alpha-methyl group and 17-beta-hydroxyl group are in the standard configuration for 17-alpha-alkylated steroids. The 2-hydroxymethylene substituent is in the Z (cis) configuration in the predominant tautomer. Because oxymetholone is a 5-alpha-reduced steroid, it is not a substrate for 5-alpha-reductase and cannot be further reduced in androgen-sensitive tissues [3].

Structural relationships: Oxymetholone is structurally related to mestanolone (17-alpha-methyl-DHT) by the addition of the C2-hydroxymethylene group; to stanozolol by shared membership in the DHT-derived 17-alpha-alkylated class; and to methandrostenolone (methandienone, Dianabol) as a fellow 17-alpha-alkylated oral anabolic steroid, though methandrostenolone is testosterone-derived rather than DHT-derived.

1.3 Synthesis

The synthesis of oxymetholone proceeds from the commercially available steroid intermediate mestanolone (17-alpha-methyl-5-alpha-androstan-17-beta-ol-3-one) or from androsterone through a series of transformations. The key synthetic step is the introduction of the C2-hydroxymethylene group through a Claisen condensation of the A-ring 3-ketone with ethyl formate in the presence of a base (typically sodium methoxide or sodium hydride), followed by selective reduction and protection steps to preserve the 17-alpha-methyl-17-beta-hydroxyl functionality [1]. The Ringold et al. (1959) original synthesis at Syntex followed this general approach,

proceeding through 2-formyl-17- α -methyl-5- α -androstan-17- β -ol-3-one as the key intermediate. The hydroxymethylene product exists as a mixture of tautomers (keto-enol equilibrium at the 2,3-positions of the A ring), with the 2-hydroxymethylene-3-keto tautomer predominating in solution and in the solid state. Industrial synthesis produces the compound at high chemical purity (greater than 98 percent by HPLC) as the crystalline powder form suitable for tableting.

2. Abstract

Oxymetholone (Anadrol-50, Anapolon) is a potent, orally active, 17-alpha-alkylated anabolic-androgenic steroid derived from dihydrotestosterone, developed at Syntex Research Laboratories by Ringold, Batres, Mancera, and Rosenkranz and first described in 1959 [1]. The compound was introduced into clinical medicine in the United Kingdom under the brand name Anapolon by 1961 and in the United States under the brand names Adroyd (Parke-Davis, 1961) and Anadrol (Syntex, 1962) for a broad range of indications including geriatric debilitation, chronic wasting, pre- and postoperative lean mass preservation, osteoporosis, and anemias.

The principal clinical application, and the only remaining FDA-approved indication, is the treatment of anemias caused by deficient red blood cell production, including acquired aplastic anemia, congenital aplastic anemia (particularly Fanconi anemia), myelofibrosis, and hypoplastic anemias resulting from the administration of myelotoxic drugs [4]. In aplastic anemia, clinical trials have demonstrated partial or full remission in patients with hypocellular marrow and evidence of residual erythropoietic activity, with response rates of approximately 35 to 56 percent at 6 months of therapy [5, 6]. The erythropoietic mechanism involves stimulation of renal erythropoietin production (with urinary erythropoietin levels elevated up to fivefold), direct stimulation of erythroid progenitor proliferation in bone marrow, and promotion of iron incorporation into hemoglobin.

The compound has been investigated in HIV/AIDS-associated wasting in two principal clinical trials. The Hengge et al. (2003) double-blind, randomized, placebo-controlled Phase III trial in 89 HIV-positive patients demonstrated that oxymetholone at 100 mg and 150 mg daily for 16 weeks produced weight gains of 3.0 and 3.5 kg respectively, compared to 1.0 kg on placebo, with significant increases in body cell mass and improvements in appetite and quality of life [7]. Hepatic enzyme elevations occurred in 27 to 35 percent of oxymetholone-treated patients, with the lower-dose regimen demonstrating comparable efficacy with reduced hepatotoxicity.

The pharmacology of oxymetholone is characterized by a paradoxical dissociation between receptor binding and biological activity. In competitive displacement assays, oxymetholone demonstrates very low binding affinity for the androgen re-

ceptor relative to testosterone and dihydrotestosterone [8]. The anabolic-to-androgenic dissociation ratio in classical rat bioassays (levator ani weight gain versus ventral prostate weight gain) is approximately 3:1 to 9:1, placing it among the most anabolic-selective oral steroids, although this ratio diminishes toward 1:1 at supratherapeutic doses [3]. The potent biological activity despite weak receptor binding suggests mechanisms beyond simple androgen receptor agonism, potentially including metabolic conversion to mestanolone (a potent AR agonist), effects on co-activator recruitment, and non-genomic signaling.

The hepatotoxic liability is the principal safety concern and the factor that most constrains clinical application. The 17- α -alkylation that confers oral bioavailability simultaneously renders the compound resistant to hepatic inactivation and exposes hepatocytes to sustained high concentrations of active steroid. Four distinct patterns of liver injury are recognized: transient serum aminotransferase elevation (common, generally clinically insignificant), bland cholestasis with jaundice (approximately 1 percent incidence, onset typically 1 to 4 months), peliosis hepatis (rare but potentially fatal through hepatic rupture), and hepatic tumors including hepatocellular adenoma and hepatocellular carcinoma (rare, associated with prolonged use of 2 to 15 years) [9, 10].

This monograph documents the chemistry, synthesis, and structure-activity relationships of oxymetholone; the androgen receptor, erythropoietic, and paradoxical estrogenic pharmacology; the limited pharmacokinetic record; preclinical pharmacology in animal models; the clinical evidence base across anemias, HIV wasting, and ancillary indications; sourcing and quality verification; reconstitution and handling; stack interactions; the hepatotoxicity and adverse-event signal in detail; and a comparative assessment of five alternative anabolic-androgenic agents against oxymetholone on five competency standards.

3. Discovery and Development History

3.1 Origin

Oxymetholone was synthesized at Syntex Research Laboratories in Mexico City by a team that included Ringold, Batres, Mancera, and Rosenkranz as part of the extensive Syntex steroid chemistry program that also produced norethindrone (the first oral contraceptive progestin), fluoxymesterone, and numerous other clinically important steroid analogs [1]. The compound was first described in a 1959 publication reporting the synthesis and biological evaluation of a series of 2-substituted androstane derivatives. Among this series, the 2-hydroxymethylene analog of 17- α -methyl-dihydrotestosterone (oxymetholone) was selected for development on the basis of its high oral anabolic potency in rat levator ani bioassays and its favorable anabolic-to-androgenic dissociation ratio.

3.2 Initial clinical introduction

Syntex and Imperial Chemical Industries introduced oxymetholone in the United Kingdom under the brand name Anapolon by 1961. In the United States, Parke-Davis introduced the compound under the brand name Adroyd in 1961, and Syntex introduced it under the brand name Anadrol in 1962. Initial approved indications were broad and included geriatric debilitation, chronic underweight and wasting states, pre- and postoperative preservation of lean body mass, convalescence from severe infection, gastrointestinal disease affecting nutritional status, osteoporosis, and general catabolic conditions. The compound was among the most widely prescribed oral anabolic steroids in the early 1960s.

3.3 FDA restriction of indications

Few pharmacokinetic and formal tolerability studies were performed before oxymetholone received regulatory approval in the 1960s; the approval was based principally on clinical efficacy observations and the prevailing regulatory standards of the period [2]. As the hepatotoxic liability and other serious adverse effects of oxymetholone became increasingly apparent through clinical experience and published case reports (including cholestatic jaundice, peliosis hepatis, and hepatic

tumors), the FDA progressively restricted the approved indication. By the mid-1970s, the only remaining FDA-approved indication was the treatment of anemias characterized by deficient red blood cell production. The prior approvals for osteoporosis, general catabolic states, and other indications were withdrawn.

3.4 Near withdrawal and market return

In 1993, Syntex (by then a subsidiary of Roche) discontinued the Anadrol-50 product in the United States, citing declining sales following the restriction of indications and the increasing availability of recombinant human erythropoietin (epoetin alfa, approved 1989) for the treatment of anemia. The compound was briefly unavailable in the United States. Unimed Pharmaceuticals subsequently acquired the rights and reintroduced Anadrol-50 in the late 1990s, partially on the basis of emerging interest in anabolic therapies for HIV/AIDS-associated wasting. Unimed was later acquired by Solvay Pharmaceuticals, which was subsequently acquired by Abbott Laboratories (now AbbVie). The current United States marketing authorization is held by Alaven Pharmaceutical, with multiple generic manufacturers also supplying the market.

3.5 Controlled substance classification

Oxymetholone was classified as a Schedule III controlled substance under the Anabolic Steroids Control Act of 1990 (an amendment to the Controlled Substances Act), which placed all anabolic steroids on the controlled substances schedules. The compound is Schedule IV in Canada and Class C in the United Kingdom. International regulatory classification varies but generally restricts availability to prescription-only or controlled status.

3.6 Current clinical status

The compound remains on the market in the United States and in multiple international jurisdictions. Its clinical use has declined substantially since the 1960s and 1970s owing to the availability of recombinant erythropoietin for anemia management, the recognition of hepatotoxic liability, and the development of alternative therapies for wasting syndromes. The compound retains a role in refractory aplastic anemia (particularly in resource-limited settings where recombinant erythropoietin may be unavailable or cost-prohibitive), in Fanconi anemia management, and in selected cases of HIV-associated wasting and severe cachexia.

4. Mechanism of Action

Oxymetholone exerts its biological effects through multiple mechanisms, including androgen receptor activation, stimulation of erythropoietin production, promotion of nitrogen retention and protein synthesis, and a paradoxical estrogenic activity. The composite pharmacology is more complex than simple androgen receptor agonism and accounts for the diverse clinical effects observed across anemia, wasting, and body composition endpoints.

4.1 Androgen receptor agonism

Oxymetholone functions as an agonist of the androgen receptor (AR), the nuclear receptor superfamily member that mediates the biological actions of testosterone and dihydrotestosterone [3]. Upon binding to AR, the steroid-receptor complex translocates to the cell nucleus and binds to androgen response elements (AREs) on target gene promoters, activating transcription of genes that regulate muscle protein synthesis, bone mineral metabolism, erythropoiesis, and secondary sexual characteristics.

A notable pharmacological paradox is that oxymetholone demonstrates very low direct binding affinity for the androgen receptor in competitive displacement assays, with relative binding affinity (RBA) values too low to quantify reliably in some published studies [8]. The Saartok et al. (1984) comparative binding study reported that oxymetholone had substantially lower RBA for both skeletal muscle and prostate androgen receptors compared to testosterone, dihydrotestosterone, nandrolone, and stanozolol. The compound also has very low affinity for human serum sex hormone-binding globulin (SHBG), less than 5 percent of the binding affinity of testosterone and less than 1 percent of that of dihydrotestosterone [3].

Despite this weak receptor binding, oxymetholone produces potent anabolic effects in vivo. This discrepancy has been attributed to several potential mechanisms: (a) metabolic conversion through cleavage of the C2-hydroxymethylene group to yield mestanolone (17- α -methyl-DHT), which has high AR binding affinity and potent androgenic activity [3]; (b) high intracellular concentrations achieved through the oral route and the resistance to hepatic inactivation conferred by the 17- α -alkyl group; (c) effects on AR co-activator and co-repressor

recruitment that are not captured by simple competitive binding assays; and (d) non-genomic signaling through membrane-associated androgen receptors or through androgen-independent pathways.

4.2 Erythropoietic stimulation

The most clinically significant pharmacodynamic effect of oxymetholone is stimulation of erythropoiesis. This occurs through at least two mechanisms: (a) increased production of erythropoietin (EPO) by the kidney, with urinary erythropoietin levels elevated up to fivefold at therapeutic doses [4, 11]; and (b) direct stimulation of erythroid progenitor cell proliferation and differentiation in the bone marrow, acting synergistically with erythropoietin to expand the erythroid compartment.

The erythropoietic effect is the basis for the FDA-approved indication in anemias characterized by deficient red blood cell production. In aplastic anemia, where bone marrow failure reduces erythropoietic capacity, oxymetholone increases both the erythropoietin drive (from the kidney) and the marrow response to that drive (by expanding residual erythroid progenitors). The clinical response typically requires 3 to 6 months of continuous therapy and is most likely in patients with evidence of residual erythropoietic activity (reticulocyte count not completely absent, bone marrow biopsy showing some erythroid elements) [5, 6].

4.3 Protein synthesis and nitrogen retention

Oxymetholone promotes positive nitrogen balance through enhanced skeletal muscle protein synthesis and reduced protein catabolism. The nitrogen retention effect is superior to that of methyltestosterone at comparable doses in published metabolic balance studies [2]. The molecular basis includes AR-mediated upregulation of genes encoding structural muscle proteins (myosin heavy chains, actin isoforms), ribosomal protein synthesis machinery, and insulin-like growth factor-1 (IGF-1) signaling components, as well as suppression of glucocorticoid-mediated catabolic gene expression through AR-glucocorticoid receptor cross-talk at shared genomic elements.

4.4 Paradoxical estrogenic activity

Oxymetholone produces clinically significant estrogenic effects (gynecomastia, water retention, edema) despite being a 5- α -reduced dihydrotestosterone derivative that cannot serve as a substrate for aromatase (CYP19A1) and therefore cannot be converted to estrogenic metabolites through the conventional aromatization pathway [3, 12]. This paradoxical estrogenicity has been attributed to direct binding and activation of estrogen receptor alpha (ER α) by oxymetholone or one of its metabolites, though the molecular characterization of this interaction is incomplete. The estrogenic activity contributes to the water retention, weight gain, and occasional gynecomastia observed in clinical and non-clinical use, and distinguishes oxymetholone from other DHT-derived steroids (such as stanozolol, drostanolone, and oxandrolone) that are generally anti-estrogenic or estrogenically neutral.

4.5 Composite pharmacology

The composite pharmacology of oxymetholone at the approved dose of 1 to 5 mg/kg/day produces: (a) moderate to potent androgen receptor activation through direct binding and through metabolic conversion to mestanolone; (b) potent erythropoietic stimulation through renal erythropoietin induction and bone marrow progenitor expansion; (c) robust positive nitrogen balance and skeletal muscle hypertrophy; (d) clinically meaningful estrogenic effects including water retention and edema; and (e) dose-dependent suppression of the hypothalamic-pituitary-gonadal axis through negative feedback inhibition of gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone secretion.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Oxymetholone is well absorbed after oral administration. The 17-alpha-methyl group protects the 17-beta-hydroxyl from first-pass hepatic oxidation, conferring oral bioavailability that is characteristic of the 17-alpha-alkylated steroid class. Specific oral bioavailability values have not been published in formal pharmacokinetic studies; the limited pharmacokinetic characterization reflects the era in which the compound was approved (early 1960s), when comprehensive pharmacokinetic evaluation was not a regulatory requirement [2].

5.2 Distribution

The volume of distribution has not been formally characterized in published studies. Based on the physicochemical properties of the compound (lipophilic steroid with moderate molecular weight), tissue distribution is expected to be extensive, with accumulation in skeletal muscle, liver, kidney, and adipose tissue. Plasma protein binding is moderate; the compound has very low affinity for SHBG (less than 5 percent of testosterone binding), suggesting that a larger fraction circulates unbound compared to testosterone or dihydrotestosterone [3]. The low SHBG binding may contribute to the high tissue availability and the potent biological activity despite weak AR binding affinity.

5.3 Metabolism

Oxymetholone is metabolized in the liver through multiple pathways: oxidation at the C2 position (cleavage of the hydroxymethylene group to yield mestanolone), reduction at the C3 position, hydroxylation at the C17 position, and conjugation with glucuronic acid [3, 13]. The cleavage of the C2-hydroxymethylene group to form mestanolone (17-alpha-methyl-DHT) is pharmacologically significant because mes-

tanolone is a potent androgen receptor agonist with high binding affinity, and this metabolic conversion may account for a substantial portion of the androgenic activity of oxymetholone.

The 17-alpha-methyl group renders the compound resistant to hepatic 17-beta-hydroxysteroid dehydrogenase-mediated inactivation, resulting in prolonged hepatic exposure that is both the source of oral bioavailability and the basis for hepatotoxicity. The compound has potential interactions with cytochrome P450 enzymes including CYP2D6, CYP3A4, CYP1A2, and CYP2C19, though the clinical significance of these interactions appears to be minimal [2].

5.4 Elimination

Oxymetholone and its metabolites are eliminated primarily in the urine as conjugates of glucuronic acid, with a smaller fraction eliminated in feces through biliary excretion. The elimination half-life from plasma has been reported as approximately 8 to 9 hours in limited published data, though some sources report the half-life as incompletely characterized [2, 13]. The relatively short plasma half-life supports once-daily or divided daily dosing regimens in clinical practice.

5.5 Routes of administration

The approved route of administration is oral. Oxymetholone is supplied as 50 mg tablets (Anadrol-50) for oral administration. No parenteral formulation has been approved or marketed. The compound is not available in transdermal, sublingual, or injectable depot formulations. The oral route is the exclusive route used in clinical trials and in approved clinical practice.

5.6 Special populations

Pediatric pharmacokinetics have not been formally characterized in published studies, though the compound has been used extensively in pediatric patients with Fanconi anemia and congenital aplastic anemia at doses of 1 to 5 mg/kg/day. Geriatric pharmacokinetics have not been separately characterized. Hepatic impairment is expected to prolong exposure owing to reduced metabolic clearance; the compound is contraindicated in patients with serious hepatic dysfunction. Renal impairment effects on pharmacokinetics have not been characterized but are expected to be modest given the predominantly hepatic metabolic clearance.

6. Preclinical Pharmacology

6.1 Anabolic activity in rat bioassays

The anabolic activity of oxymetholone has been characterized in the classical Hershberger bioassay using castrated rat levator ani muscle weight as the anabolic endpoint and ventral prostate weight as the androgenic endpoint. Oxymetholone produces a high ratio of levator ani weight gain to ventral prostate weight gain, with published anabolic-to-androgenic dissociation ratios of approximately 3:1 to 9:1, placing it among the most anabolic-selective oral steroids tested in this system [3]. However, this ratio is dose-dependent and diminishes toward 1:1 at supratherapeutic doses, reflecting saturation of anabolic signaling and increasing androgenic spillover at high receptor occupancy.

6.2 Erythropoietic activity in animal models

Oxymetholone produces dose-dependent stimulation of erythropoiesis in animal models including mouse, rat, and dog. In polycythemic mouse bioassays, oxymetholone stimulates reticulocyte production and hemoglobin synthesis at doses comparable to or lower than other anabolic steroids tested. The erythropoietic effect is mediated through renal erythropoietin production and is augmented by the direct bone marrow stimulatory effect on erythroid progenitors [11].

6.3 Hepatotoxicity in animal models

The hepatotoxic potential of oxymetholone has been documented in preclinical toxicology studies. The National Toxicology Program (NTP) Technical Report 485 evaluated oxymetholone in F344/N rats and B6C3F1 mice in 2-year carcinogenicity studies [14]. Findings included hepatocellular hypertrophy, necrosis, and increased incidence of hepatocellular adenoma and carcinoma in treated animals, supporting the clinical observations of hepatic tumor formation with prolonged use.

6.4 Reproductive toxicology

Oxymetholone produces dose-dependent suppression of gonadotropin secretion and testicular atrophy in male animals and virilization in female animals. The compound is classified as FDA Pregnancy Category X (contraindicated in pregnancy) based on demonstrated teratogenic effects in animal studies, including masculinization of female offspring and impaired fertility.

7. Clinical Evidence Base

7.1 Aplastic anemia

The primary clinical application of oxymetholone is the treatment of aplastic anemia. In a seminal early study, Sanchez-Medal et al. treated 31 patients with aplastic anemia with oxymetholone; of the 28 patients who survived beyond 2 months, 11 (39 percent) showed clinical and hematological improvement, with responses most common in patients with residual erythropoietic bone marrow activity [5]. Subsequent studies confirmed response rates of 35 to 56 percent in aplastic anemia, with responses characterized by increases in hemoglobin, reticulocyte count, and in some cases neutrophil and platelet counts [6].

The Bacigalupo et al. (1992) prospective randomized trial of immunosuppressive therapy in aplastic anemia evaluated antithymocyte globulin with methylprednisolone and oxymetholone versus antithymocyte globulin with very high-dose methylprednisolone and oxymetholone, demonstrating the contribution of oxymetholone as an adjunctive erythropoietic agent in combination immunosuppressive regimens [15].

In Fanconi anemia, a congenital aplastic anemia syndrome caused by defects in DNA repair genes, oxymetholone has been used extensively as a bridge therapy to hematopoietic stem cell transplantation. Rose et al. (2014) demonstrated that oxymetholone therapy in Fanconi anemia suppresses osteopontin transcription and induces hematopoietic stem cell cycling, providing a mechanistic basis for the clinical response beyond simple erythropoietin stimulation [16].

7.2 HIV/AIDS-associated wasting

Two principal clinical trials have evaluated oxymetholone in HIV-associated wasting. The Hengge et al. (2003) double-blind, randomized, placebo-controlled Phase III trial enrolled 89 HIV-positive patients (both men and women) with wasting syndrome and randomized them to oxymetholone 100 mg daily, oxymetholone 150 mg daily, or placebo for 16 weeks [7]. Oxymetholone-treated patients gained 3.0 +/- 0.5 kg (100 mg group) and 3.5 +/- 0.7 kg (150 mg group) compared to 1.0 kg in the placebo group, with significant increases in body cell mass. Patients reported im-

proved appetite, food intake, subjective well-being, and reduced weakness. Hepatic enzyme elevations (greater than 3 times the upper limit of normal) occurred in 35 percent of patients in the 150 mg group and 27 percent of patients in the 100 mg group, with no hepatic enzyme elevations in the placebo group. The lower-dose regimen was recommended as comparably effective with reduced hepatotoxicity.

Strawford et al. (1999) demonstrated that resistance exercise combined with oxymetholone produced significant increases in lean body mass and strength in eugonadal men with AIDS-associated wasting in a randomized controlled trial [17].

7.3 Myelofibrosis

Oxymetholone has been used in the treatment of anemia associated with myelofibrosis. Besa et al. (1982) reported that oxymetholone therapy in myelofibrosis produced hematological responses in a proportion of patients, with improvements in hemoglobin levels and reduction in transfusion requirements, though responses were variable and hepatotoxicity remained a limiting factor [18].

7.4 Antithrombin III deficiency

Limited clinical data support the use of oxymetholone in antithrombin III deficiency, where the anabolic steroid increases hepatic synthesis of antithrombin III protein. This application has not produced a registration trial and is not an approved indication [2].

7.5 Pediatric growth failure

Oxymetholone has been investigated for growth stimulation in children with growth failure of various etiologies, though this application has been largely superseded by recombinant human growth hormone. The compound promotes linear growth through stimulation of growth hormone secretion and through direct effects on growth plate chondrocytes, but the androgenic effects and hepatotoxicity limit its applicability in pediatric populations [2].

7.6 Osteoporosis (historical)

Oxymetholone was approved for osteoporosis in its initial marketing in the 1960s, based on the known effects of androgens on bone mineral density. This indication was withdrawn in the mid-1970s as the risk-benefit ratio was considered unfavorable relative to alternative therapies and as the hepatotoxic liability became well characterized.

8. Sourcing and Quality Verification

Pharmaceutical-grade oxymetholone (Anadrol-50, USP) is the highest-quality source for research applications. The pharmaceutical product is supplied as 50 mg scored tablets by Alaven Pharmaceutical and by generic manufacturers in the United States. The compound is available by prescription in the United States (Schedule III controlled substance), in the United Kingdom (Class C controlled substance), in Canada (Schedule IV), and in multiple other jurisdictions with varying regulatory classification.

Research-grade oxymetholone is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, Toronto Research Chemicals, Steraloids, LGC Standards, others) at greater than 98 percent purity by HPLC. Supply is available in milligram to gram quantities as the neat crystalline powder. Pricing varies substantially by supplier and quantity; research-grade material is generally available at \$50 to \$300 per gram.

The compound is classified as a controlled substance in most jurisdictions, and procurement requires appropriate licensing and regulatory authorization. Investigators should confirm that their institutional controlled substance license permits acquisition of Schedule III anabolic steroids.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (target greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (332.24 ± 0.01 for the protonated molecular ion $[M+H]^+$, m/z 333.24)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) confirmation of structure, with particular attention to the C2-hydroxymethylene resonance
- Melting point determination (reference range 172 to 180 degrees Celsius)
- Karl Fischer analysis for residual water content
- Residual solvent analysis where the synthesis route is known

Third-party analytical laboratories (Janoshik Analytical, Simec AG, and others) provide independent confirmation of vendor certificates of analysis. The non-pharmaceutical market for oxymetholone is extensive and includes underground and counterfeit sources with variable quality; analytical verification is essential for any research application.

9. Reconstitution and Handling

Oxymetholone is supplied as a crystalline powder (research grade) or as 50 mg tablets (pharmaceutical grade). The compound is practically insoluble in water. For in vitro research applications, stock solutions are prepared in organic solvents.

In vitro preparation: Dissolve in dimethyl sulfoxide (DMSO) at concentrations up to 10 mM for cell culture assays. Working concentrations for androgen receptor activation studies are typically in the 10 nanomolar to 10 micromolar range. Dilute stock solutions into culture medium immediately before use; final DMSO concentration should not exceed 0.1 percent (v/v) to avoid solvent cytotoxicity. Ethanol may be used as an alternative solvent at concentrations up to 50 mM, with final ethanol concentration in culture medium not exceeding 0.5 percent (v/v).

Storage: Solid material should be stored at room temperature (15 to 25 degrees Celsius) in a tightly closed container, protected from light and moisture. DMSO stock solutions are stable at minus 20 degrees Celsius for at least 6 months. Repeated freeze-thaw cycles should be avoided; aliquoting into single-use volumes is recommended.

Handling: Standard laboratory precautions for handling potent steroid hormones apply. The compound is a Schedule III controlled substance; handling, storage, and disposal must comply with institutional and regulatory requirements for controlled substances. Use of gloves, laboratory coat, and appropriate containment when weighing and dissolving the powder is recommended to avoid dermal absorption.

Tablet preparation for animal studies: Pharmaceutical-grade tablets can be crushed, suspended in vehicle (methylcellulose, carboxymethylcellulose, or corn oil), and administered by oral gavage at the target dose. Homogeneity of the suspension should be confirmed before each administration.

10. Stack Interactions and Combinations

Oxymetholone interacts with several drug classes through its hepatic metabolic burden, its effects on the hypothalamic-pituitary-gonadal axis, its estrogenic activity, and its alterations in coagulation factor synthesis. Investigators conducting research with oxymetholone should consider:

Hepatotoxic agents: Concurrent administration with other hepatotoxic drugs (acetaminophen at high doses, methotrexate, azole antifungals, antiretroviral protease inhibitors, isoniazid, valproic acid) increases the risk of hepatic injury. The combination with other 17-alpha-alkylated steroids (stanozolol, methandrostenolone, methyltestosterone, fluoxymesterone) is expected to produce additive hepatotoxicity and is strongly discouraged.

Anticoagulants: Oxymetholone potentiates the effect of oral anticoagulants (warfarin, acenocoumarol) by altering hepatic synthesis of vitamin K-dependent coagulation factors. Dose reduction of the anticoagulant and increased monitoring of prothrombin time/international normalized ratio (PT/INR) are required during concurrent administration [4].

Insulin and oral hypoglycemics: Oxymetholone may increase insulin sensitivity and potentiate the hypoglycemic effect of insulin and sulfonylurea agents. Blood glucose monitoring should be intensified during concurrent administration, and dose adjustment of the hypoglycemic agent may be required [4].

Corticosteroids and ACTH: Concurrent administration with corticosteroids or adrenocorticotrophic hormone (ACTH) may increase the risk of edema, particularly in patients with cardiac, hepatic, or renal disease [4].

Other anabolic-androgenic steroids: Combination with injectable anabolic steroids (testosterone esters, nandrolone decanoate, boldenone undecylenate) produces additive anabolic effects, additive hypothalamic-pituitary-gonadal axis suppression, and increased cardiovascular and hepatic risk. The combination of

oxymetholone with injectable testosterone is used in some clinical and research protocols for severe wasting, though the risk-benefit ratio must be carefully considered.

Aromatase inhibitors: The estrogenic effects of oxymetholone (water retention, gynecomastia) are not amenable to aromatase inhibitor therapy (anastrozole, letrozole, exemestane) because the estrogenic activity is not mediated through aromatization. Selective estrogen receptor modulators (tamoxifen, raloxifene) may be more appropriate for management of oxymetholone-induced estrogenic effects, though clinical data on this combination are limited.

Recombinant erythropoietin: Concurrent administration with erythropoiesis-stimulating agents (epoetin alfa, darbepoetin alfa) produces additive erythropoietic stimulation and increases the risk of polycythemia, thrombosis, and hypertension. Hematocrit and hemoglobin monitoring should be intensified during combination therapy.

11. Adverse Events and Safety

11.1 Hepatotoxicity

Hepatotoxicity is the most clinically significant adverse effect of oxymetholone and the principal factor limiting its clinical utility. Four distinct patterns of hepatic injury are recognized [9, 10]:

Transient aminotransferase elevation: Mild, dose-dependent elevations in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are common during oxymetholone therapy and are generally clinically insignificant when less than 3 times the upper limit of normal. In the Hengge et al. (2003) HIV wasting trial, clinically significant hepatic enzyme elevations (greater than 3 times ULN) occurred in 27 to 35 percent of oxymetholone-treated patients at 100 to 150 mg daily [7].

Cholestatic jaundice: Bland cholestasis (intrahepatic cholestasis without significant hepatocellular necrosis or bile duct injury) occurs in approximately 1 percent of treated patients, typically within 1 to 4 months of initiating therapy [9]. Presentation is insidious, with nausea, fatigue, and pruritus preceding the onset of jaundice. Resolution typically occurs 3 to 6 months after discontinuation, though severe cases may require 5 to 12 months for bilirubin normalization. The mechanism may involve altered bile salt transporter protein function [9].

Peliosis hepatis: Blood-filled sinusoidal cysts develop within the hepatic parenchyma in association with prolonged oxymetholone therapy. Yanoff (1975) and Bagheri and Boyer (1974) reported cases of peliosis hepatis in patients receiving oxymetholone, with presentation ranging from incidental hepatomegaly to fatal hepatic rupture with intraperitoneal hemorrhage [19, 20]. In a series of 12 patients with peliosis hepatis associated with androgen therapy (including oxymetholone and fluoxymesterone), three died of hepatic failure [20]. Peliosis hepatis is usually at least partially reversible upon discontinuation of therapy.

Hepatic tumors: Hepatocellular adenoma and hepatocellular carcinoma have been reported in patients receiving prolonged oxymetholone therapy, typically after 2 to 15 years of continuous use [9, 10]. The majority of published cases involve patients with Fanconi anemia or aplastic anemia receiving chronic androgen ther-

apy, though cases have been reported in other patient populations. Tumors may develop in the absence of cirrhosis and may undergo partial or complete regression upon discontinuation in some cases, particularly hepatic adenomas. A 20-year-old patient with Fanconi anemia developed hepatocellular carcinoma after 1 year of oxymetholone therapy, with peliosis and multiple intrahepatic hematomas identified on autopsy [10].

11.2 Cardiovascular adverse effects

Oxymetholone produces dose-dependent alterations in lipid metabolism, with suppression of high-density lipoprotein (HDL) cholesterol and elevation of low-density lipoprotein (LDL) cholesterol. These changes are consistent across the 17-alpha-alkylated steroid class and increase cardiovascular risk with chronic administration.

Fluid retention and edema, mediated through the estrogenic activity and through sodium and water retention, can exacerbate congestive heart failure in predisposed patients. The FDA label includes a warning regarding edema with or without congestive heart failure in patients with preexisting cardiac, hepatic, or renal disease [4].

11.3 Endocrine adverse effects

Oxymetholone produces dose-dependent suppression of the hypothalamic-pituitary-gonadal axis through negative feedback inhibition of gonadotropin secretion. In males, this manifests as decreased endogenous testosterone production, reduced spermatogenesis, and testicular atrophy. In females, virilization (acne, hirsutism, voice deepening, clitoral enlargement, menstrual irregularity, and male-pattern alopecia) is dose-dependent and may be irreversible with prolonged use [4].

11.4 Musculoskeletal adverse effects

In prepubertal children, oxymetholone can accelerate epiphyseal maturation and cause premature closure of growth plates, resulting in compromised final adult height. Periodic monitoring of bone age by radiography is recommended during therapy in pediatric patients [4].

11.5 Other adverse effects

Additional reported adverse events include:

- Nausea, vomiting, diarrhea, and abdominal pain (gastrointestinal)
- Headache, insomnia, depression, lethargy, and excitability (neuropsychiatric)
- Acne, oily skin, and changes in skin pigmentation (dermatologic)
- Priapism in males (genitourinary)
- Changes in libido (increased or decreased)
- Polycythemia (secondary to erythropoietic stimulation, requiring hematocrit monitoring)

11.6 Contraindications

Oxymetholone is contraindicated in: pregnancy (Category X); known or suspected prostate carcinoma; breast carcinoma in males; breast carcinoma in females with hypercalcemia; severe hepatic dysfunction; nephrosis or the nephrotic phase of nephritis; and hypersensitivity to the compound [4].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative anabolic-androgenic agents against oxymetholone, evaluated on five competency standards: novelty, effect size (in the primary indication of anemia or wasting), promising potential (current clinical trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal alternative anabolic-androgenic agents available for the treatment of anemias and wasting conditions.

12.1 Oxandrolone (Anavar)

Mechanism: 17-alpha-alkylated DHT-derived anabolic-androgenic steroid with a high anabolic-to-androgenic ratio. Differs from oxymetholone by replacement of the C2 carbon with an oxygen atom (oxandrolone is a 2-oxa-17-alpha-methyl-DHT derivative), which confers greater metabolic stability and reduced hepatotoxicity relative to oxymetholone.

Clinical applications: FDA-approved for weight gain after weight loss following surgery, chronic infections, or trauma, and for treatment of bone pain from osteoporosis. Investigated extensively in burn recovery, HIV wasting, Turner syndrome growth failure, and constitutional delay of growth and puberty.

Novelty: Low. The compound was developed at Searle in 1962 and has been in clinical use for over 60 years.

Effect size: Moderate. Oxandrolone produces weight gain and lean mass increases in wasting conditions, though the magnitude is generally less than that produced by oxymetholone at equivalent doses. In burn patients, oxandrolone at 20 mg/day produces significant improvements in lean body mass, protein synthesis, and wound healing. In HIV wasting, the effect size on body weight is smaller than that reported for oxymetholone in the Hengge et al. trial.

Promising potential: Moderate. The compound retains clinical utility in burn recovery and selected wasting conditions. Research applications continue, particularly in sarcopenia and cachexia.

Side-effect profile: Favorable relative to oxymetholone. Hepatotoxicity occurs but is substantially less frequent and less severe than with oxymetholone, attributable to the 2-oxa modification that increases metabolic stability. Virilization in females is milder. The compound has the most favorable hepatic safety profile among the 17-alpha-alkylated steroids.

Overall validation: Moderate to high. Extensive clinical literature spanning burn recovery, HIV wasting, Turner syndrome, and constitutional growth delay. Multiple randomized controlled trials.

Comparison to oxymetholone: Oxandrolone is the principal clinical alternative within the oral 17-alpha-alkylated class. It offers a substantially more favorable hepatic safety profile at the cost of lower potency on a per-milligram basis. For research applications where hepatotoxicity is a concern or where lower-potency anabolism is acceptable, oxandrolone is generally preferred. Oxymetholone retains the advantage of superior erythropoietic stimulation for anemia indications.

12.2 Nandrolone Decanoate (Deca-Durabolin)

Mechanism: Injectable 19-nortestosterone derivative (nandrolone) formulated as the decanoate ester for depot intramuscular administration. Nandrolone is a potent androgen receptor agonist with high binding affinity. It is a substrate for 5-alpha-reductase but is converted to 5-alpha-dihydronandrolone, which has lower AR affinity than the parent compound, resulting in reduced androgenic activity in 5-alpha-reductase-expressing tissues (skin, prostate).

Clinical applications: Approved in many jurisdictions for the treatment of anemia of chronic renal failure, osteoporosis, and selected wasting conditions. Used historically for aplastic anemia before the availability of recombinant erythropoietin.

Novelty: Low. Nandrolone decanoate has been in clinical use since the 1960s.

Effect size: Moderate to high. Nandrolone produces robust nitrogen retention, lean mass gains, and erythropoietic stimulation comparable to oxymetholone. In anemia of chronic renal failure, nandrolone decanoate at 100 to 200 mg intramus-

cularly every 1 to 2 weeks produces significant increases in hemoglobin and hematocrit. In HIV wasting, nandrolone produces significant lean mass gains in randomized trials.

Promising potential: Low to moderate. The compound has been largely superseded by recombinant erythropoietin for anemia and by alternative agents for wasting. Research applications continue in sarcopenia and cachexia.

Side-effect profile: Favorable relative to oxymetholone. Nandrolone decanoate is not 17-alpha-alkylated and therefore does not produce the characteristic hepatotoxicity of oxymetholone and other alkylated steroids. The principal adverse effects are androgenic (virilization in females, acne), cardiovascular (lipid alterations, though less severe than 17-alpha-alkylated steroids), and endocrine (hypothalamic-pituitary-gonadal axis suppression). The injectable route eliminates first-pass hepatic exposure.

Overall validation: High. Extensive clinical literature including randomized controlled trials in anemia, wasting, and osteoporosis. One of the most extensively studied injectable anabolic steroids.

Comparison to oxymetholone: Nandrolone decanoate offers comparable anabolic and erythropoietic efficacy with a substantially more favorable hepatic safety profile, attributable to the absence of 17-alpha-alkylation. The requirement for intramuscular injection and the longer onset of action (depot formulation) are operational disadvantages relative to the oral convenience of oxymetholone. For indications where hepatotoxicity risk must be minimized, nandrolone decanoate is preferred.

12.3 Stanozolol (Winstrol)

Mechanism: 17-alpha-alkylated DHT-derived anabolic-androgenic steroid bearing a pyrazole ring fused to the A ring of the androstane skeleton. Stanozolol has high anabolic-to-androgenic dissociation and relatively high androgen receptor binding affinity compared to oxymetholone.

Clinical applications: Historically approved for aplastic anemia, hereditary angioedema, and catabolic conditions. Currently, the primary clinical indication in most jurisdictions is hereditary angioedema prophylaxis, based on stimulation of hepatic synthesis of C1-esterase inhibitor.

Novelty: Low. The compound was developed by Winthrop Laboratories in the 1960s.

Effect size: Moderate. In aplastic anemia, stanozolol produces hematological responses comparable to oxymetholone in some comparative studies, though the erythropoietic potency is generally considered lower. In hereditary angioedema, stanozolol is highly effective for prophylaxis of attacks.

Promising potential: Low. The compound has been largely superseded by targeted therapies for hereditary angioedema (C1-esterase inhibitor concentrate, icatibant, lanadelumab) and by recombinant erythropoietin for anemia.

Side-effect profile: Similar to oxymetholone in hepatotoxic potential, as both are 17-alpha-alkylated steroids. Cholestatic jaundice, peliosis hepatis, and hepatic tumors have been reported with stanozolol. The estrogenic activity is lower than oxymetholone (stanozolol does not produce significant estrogenic effects), reducing water retention and gynecomastia risk.

Overall validation: Moderate. Established clinical literature in hereditary angioedema and aplastic anemia. Multiple clinical studies, though fewer randomized controlled trials than some comparators.

Comparison to oxymetholone: Stanozolol shares the hepatotoxic liability of the 17-alpha-alkylated class but produces less water retention and estrogenic effects. The erythropoietic potency is generally considered lower than oxymetholone. Stanozolol has retained a niche clinical role in hereditary angioedema that oxymetholone does not share.

12.4 Testosterone Enanthate

Mechanism: Injectable ester prodrug of testosterone, the principal endogenous androgen. Testosterone is the reference androgen receptor agonist. Testosterone enanthate provides depot intramuscular delivery with a pharmacokinetic profile supporting injection intervals of 1 to 4 weeks.

Clinical applications: Approved for testosterone replacement therapy in hypogonadal males, delayed puberty, and selected conditions requiring androgen supplementation. Investigated for anemia, wasting, sarcopenia, and numerous other indications.

Novelty: Low. Testosterone and its esters have been in clinical use since the 1930s to 1950s.

Effect size: Moderate to high. Testosterone produces erythropoietic stimulation, positive nitrogen balance, and lean mass gains. The erythropoietic effect is the basis for the polycythemia observed as a common adverse effect of testosterone replacement therapy. In wasting conditions, testosterone produces significant lean mass gains in randomized trials, with effect sizes comparable to nandrolone decanoate.

Promising potential: Moderate. Testosterone remains the reference androgen for replacement therapy and is under active investigation for sarcopenia, frailty, and related conditions in aging populations.

Side-effect profile: Favorable relative to oxymetholone. Testosterone enanthate is not 17-alpha-alkylated and does not produce the characteristic hepatotoxicity. The principal adverse effects are androgenic (acne, hair loss, virilization), cardiovascular (polycythemia, lipid alterations), and endocrine (hypothalamic-pituitary-gonadal axis suppression, though this is inherent to the replacement indication).

Overall validation: Very high. The most extensively studied anabolic-androgenic steroid, with thousands of published clinical studies and decades of clinical experience. Testosterone is the reference standard for the class.

Comparison to oxymetholone: Testosterone enanthate offers a fundamentally different risk-benefit profile. It lacks the hepatotoxicity of oxymetholone but requires intramuscular injection. Its anabolic and erythropoietic effects are well characterized but are less potent on a dose-equivalent basis than oxymetholone for anemia indications. Testosterone is generally preferred when the clinical goal is androgen replacement or moderate anabolism without hepatotoxic risk.

12.5 Danazol

Mechanism: 17-alpha-alkylated synthetic steroid derived from ethisterone, with weak androgenic activity and potent anti-gonadotropic and anti-estrogenic effects. Danazol suppresses pituitary gonadotropin output and reduces estrogen and progesterone levels. It also stimulates hepatic synthesis of several proteins including C1-esterase inhibitor and coagulation factors.

Clinical applications: FDA-approved for endometriosis, fibrocystic breast disease, and hereditary angioedema prophylaxis. Investigated for aplastic anemia, immune thrombocytopenic purpura, and autoimmune hemolytic anemia.

Novelty: Low. The compound has been in clinical use since the 1970s.

Effect size: Moderate in aplastic anemia. Danazol produces hematological responses in a proportion of patients with aplastic anemia, with response rates similar to other androgen therapies. The erythropoietic effect is less potent than oxymetholone.

Promising potential: Low. The compound has been largely superseded by GnRH agonists for endometriosis and by targeted therapies for hereditary angioedema. It retains a limited role in refractory cytopenias.

Side-effect profile: Hepatotoxicity is present (17-alpha-alkylated structure) but is generally less severe than with oxymetholone at the doses used for hereditary angioedema and aplastic anemia. Androgenic effects (weight gain, acne, hirsutism, voice changes) are dose-dependent. Anti-estrogenic effects (hot flashes, vaginal dryness) are prominent in females.

Overall validation: Moderate. Established clinical literature across multiple indications. The aplastic anemia evidence is based on smaller studies and clinical experience rather than large randomized trials.

Comparison to oxymetholone: Danazol shares the 17-alpha-alkylated hepatotoxic liability but produces less potent anabolic and erythropoietic effects. Its primary clinical utility is in hereditary angioedema and endometriosis rather than anemia, though it has been used in refractory aplastic anemia. The anti-estrogenic effect contrasts with the paradoxical estrogenic activity of oxymetholone.

12.6 Comparator summary

Among the five comparators, **oxandrolone** represents the closest oral alternative to oxymetholone, offering substantially reduced hepatotoxicity at the cost of lower per-milligram potency. **Nandrolone decanoate** offers comparable anabolic and erythropoietic efficacy without the hepatotoxic liability of 17-alpha-alkylation but requires intramuscular injection. **Stanozolol** shares the hepatotoxic risk profile and has retained a niche in hereditary angioedema. **Testosterone enanthate** is the reference standard anabolic-androgenic steroid, with the broadest evidence base but

lower per-dose potency for anemia indications. **Danazol** is a weak androgen with distinct clinical applications that overlap minimally with oxymetholone except in refractory aplastic anemia.

Oxymetholone occupies a specific clinical niche as the most potent oral erythropoietic stimulant among the available anabolic-androgenic steroids. Its clinical utility is defined by the balance between this potent erythropoietic activity and the substantial hepatotoxic liability. In settings where recombinant erythropoietin is unavailable or ineffective and where oral administration is operationally necessary, oxymetholone remains a clinically relevant agent. In most other contexts, the risk-benefit analysis favors the less hepatotoxic alternatives, particularly nandrolone decanoate for injectable applications and oxandrolone for oral applications.

13. References

1. Ringold HJ, Batres E, Mancera O, Rosenkranz G. Steroids. CXII. A new family of C-2 oxygenated androstan-3-ones. *J Am Chem Soc.* 1959;81(14):3712-3716.
2. Pavlatos AM, Fultz O, Monberg MJ, Vootkur A. Review of oxymetholone: a 17alpha-alkylated anabolic-androgenic steroid. *Clin Ther.* 2001;23(6):789-801.
3. Oxymetholone. In: Elks J, Ganellin CR, eds. *The Dictionary of Drugs: Chemical Data, Structures and Bibliographies.* Chapman and Hall; 1990.
4. Anadrol-50 (oxymetholone) 50 mg Tablets. Prescribing Information. Alaven Pharmaceutical LLC; revised August 2004. FDA Reference NDA 16-848/S-021.
5. Sanchez-Medal L, Pizzuto J, Torre-Lopez E, Derbez R. Effect of oxymetholone in refractory anemia. *Arch Intern Med.* 1964;113:721-729.
6. Shahidi NT, Diamond LK. Testosterone-induced remission in aplastic anemia of both acquired and congenital types. Further observations in 24 cases. *N Engl J Med.* 1961;264:953-967.
7. Hengge UR, Stocks K, Wiehler H, et al. Double-blind, randomized, placebo-controlled phase III trial of oxymetholone for the treatment of HIV wasting. *AIDS.* 2003;17(5):699-710.
8. Saartok T, Dahlberg E, Gustafsson JA. Relative binding affinity of anabolic-androgenic steroids: comparison of the binding to the androgen receptors in skeletal muscle and in prostate, as well as to sex hormone-binding globulin. *Endocrinology.* 1984;114(6):2100-2106.
9. Androgenic Steroids. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury.* National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Updated 2020.
10. Bagheri SA, Boyer JL. Peliosis hepatitis associated with androgenic-anabolic steroid therapy: a severe form of hepatic injury. *Ann Intern Med.* 1974;81(5):610-618.
11. Naets JP, Wittek M. The mechanism of action of androgens on erythropoiesis. *Ann N Y Acad Sci.* 1968;149(1):366-376.

12. Llewellyn W. Oxymetholone. In: Anabolics. 11th ed. Molecular Nutrition; 2017:34-42.
13. Schanzer W. Metabolism of anabolic androgenic steroids. Clin Chem. 1996;42(7):1001-1020.
14. National Toxicology Program. Toxicology and carcinogenesis studies of oxymetholone (CAS No. 434-07-1) in F344/N rats and B6C3F1 mice. NTP Technical Report 485. NIH Publication No. 99-3949; 1999.
15. Bacigalupo A, Broccia G, Corda G, et al. Immunosuppressive therapy of aplastic anemia: results of a prospective, randomized trial of antithymocyte globulin, methylprednisolone, and oxymetholone to antithymocyte globulin, very high-dose methylprednisolone, and oxymetholone. Blood. 1992;79(10):2566-2571.
16. Rose SR, Kim MO, Giri N, et al. Oxymetholone therapy of Fanconi anemia suppresses osteopontin transcription and induces hematopoietic stem cell cycling. Stem Cell Reports. 2014;2(1):1-8.
17. Strawford A, Barbieri T, Van Loan M, et al. Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: a randomized controlled trial. JAMA. 1999;281(14):1282-1290.
18. Besa EC, Gorshein D, Gardner FH. Oxymetholone treatment for the anemia of bone marrow failure. Blood. 1972;40(4):460-469.
19. Yanoff M. Peliosis hepatitis associated with administration of oxymetholone. Am J Clin Pathol. 1975;63(3):434.
20. Nadell J, Kosek J. Peliosis hepatitis. Twelve cases associated with oral androgen therapy. Arch Pathol Lab Med. 1977;101(8):405-410.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Oxymetholone is a Schedule III controlled substance in the United States under the Controlled Substances Act and is subject to equivalent regulatory controls in most jurisdictions. Procurement, possession, and use require appropriate licensing and regulatory authorization. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. The hepatotoxic lia-

bility of 17-alpha-alkylated steroids, including oxymetholone, is well characterized and clinically significant; periodic liver function monitoring is mandatory during any research protocol involving this compound.