REVIEW ARTICLE

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The Anabolic Androgenic Steroid Oxandrolone in the Treatment of Wasting and Catabolic Disorders

Review of Efficacy and Safety

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Abstract

There has been increasing interest in the development of effective agents that can be safely used to promote anabolism in the clinical setting for patients with chronic wasting conditions as well as in the prevention and treatment of frailty associated with loss of muscle tissue in aging (sarcopenia).

One such agent is the anabolic androgenic steroid (AAS) oxandrolone, which has been used in such clinical situations as HIV-related muscle wasting, severe burn injury, trauma following major surgery, neuromuscular disorders and alco-

holic hepatitis for over 30 years. In the US, oxandrolone is the only AAS that is US FDA-approved for restitution of weight loss after severe trauma, major surgery or infections, malnutrition due to alcoholic cirrhosis, and Duchenne's or Becker's muscular dystrophy.

Our review of the use of oxandrolone in the treatment of catabolic disorders, HIV and AIDS-related wasting, neuromuscular and other disorders provides strong evidence of its clinical efficacy. Improvements in body composition, muscle strength and function, status of underlying disease or recovery from acute catabolic injury and nutritional status are significant in the vast majority of well designed trials. However, oxandrolone has not yet been studied in sarcopenia.

Unlike other orally administered C17α-alkylated AASs, the novel chemical configuration of oxandrolone confers a resistance to liver metabolism as well as marked anabolic activity. In addition, oxandrolone appears not to exhibit the serious hepatotoxic effects (jaundice, cholestatic hepatitis, peliosis hepatis, hyperplasias and neoplasms) attributed to the C17α-alkylated AASs. Oxandrolone is reported to be generally well tolerated and the most commonly documented adverse effects are transient elevations in transaminase levels and reductions in high density lipoprotein cholesterol level.

However, optimal risk **:** benefit ratios for oxandrolone and other agents in its class will need to be refined before widespread clinical acceptance of AASs as a therapeutic option in sarcopenia and other chronic wasting conditions.

There has been increasing interest in the development of effective agents with good safety to promote anabolism in the clinical setting for patients with chronic wasting conditions as well as in the prevention and treatment of frailty associated with loss of muscle tissue in aging (sarcopenia). In this review we focus on a particular anabolic steroid, oxandrolone, which has been used in such clinical situations for over 30 years. We review the evidence of its clinical efficacy in acute catabolic disorders, such as burns, chronic catabolic disorders, HIV/AIDS-associated wasting, neuromuscular and other disorders, along with the potential toxicity of this class of anabolic steroids in general, as well as that attributable to oxandrolone itself. Discussion of the utility of this agent and direction for future research in sarcopenia and other chronic wasting disorders is provided.

1. Overview of Anabolic Androgenic Steroids (AASs)

Since anabolic androgenic steroids (AASs) are derivatives or structural modifications of the parent steroid hormone, testosterone, they exhibit both anabolic and androgenic activity. Anabolic effects are the positive action of testosterone to promote protein synthesis, nitrogen retention and skeletal muscle growth. Androgenic effects are the development and maintenance of primary and secondary sexual characteristics in males. In females, androgenic effects are evident as male pattern baldness, deepened voice, clitoromegaly and growth of facial hair.

AASs mostly induce their responses at various tissues via a single androgen receptor (AR), a 120 kDa cytosolic protein encoded on the X chromosome.[1] At the cellular level, AASs pass through the cell membrane of the target tissue and bind to an AR in the cytosol. In the cell, testosterone itself may be converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase. Either testosterone or DHT can bind to the AR. The AR complex is transferred to the nucleus and binds to DNA, stimulating protein synthesis. The new proteins mediate the function of the hormone. Attempts to isolate a purely anabolic steroid have been unsuccessful as ARs are present in reproductive and non-reproductive tissues; no sin-

gular anabolic or androgenic receptor exists. The diverse activity of AASs are the result of different relative binding affinities to ARs in various tissues and/or the number of androgen-binding sites per milligram protein.[1,2]

The anabolic actions of AASs occur through direct and indirect mechanisms. Anabolic steroids directly increase muscle mass by inducing protein synthesis and efficient utilisation of amino acids and by increasing AR expression in skeletal muscle.[1] Short-term administration of oxandrolone to healthy young men increased fractional synthesis of muscle protein by 44%.[3] Hypogonadal men treated with testosterone displayed enhanced skeletal muscle mass due to increased mixed muscle protein and myosin heavy chain (MHC) synthesis rates.[4] Short-term resistance training in 78- to 84-year-old men also demonstrated similar effects on mixed muscle and MHC protein synthesis rates.[5]

AASs act indirectly by antagonism of the glucocorticoid receptor, similar in structure to the AR. Competitive binding to the glucocorticoid receptor inhibits protein catabolism. Testosterone administration to patients with severe burns significantly reduced muscle catabolism.[6] An inductive effect of AASs on hepatic insulin-like growth factor (IGF)-1 production is also reported to enhance skeletal muscle protein synthesis. Increased IGF-1 mRNA levels were observed in hypogonadal men treated with testosterone.[7] In addition, suppression of myostatin protein expression by AASs appears to influence muscle anabolism in humans.[1]

The use of AASs in the athletic community, for their purported enhancement of muscle mass and strength, has been widely documented, despite limited supporting evidence.[8] Bhasin et al.[9] were able to demonstrate in a randomised, double-blind, placebo-controlled trial that, when supraphysiological doses of testosterone were given to healthy men for 10 weeks with and without resistance training, the effect of testosterone was additive to that of resistance training, resulting in increased fat-free mass, muscle size and strength. A recent review of testosterone supplementation trials in older men with low-normal or mildly decreased testosterone levels suggested that benefits most uniformly seen are in the area of body composition, with variable effects on muscle function, functional limitations, sexual performance, mood and cognition.[10]

The notion of AASs as an alternative treatment to promote anabolism in a number of diseases and disorders characterised by sarcopenia is currently under investigation. Oxandrolone is one such AAS treatment that has been used for over 30 years, with demonstrated improved clinical outcomes in both acute catabolic and chronic disease.

2. Oxandrolone

2.1 Structure

Oxandrolone, first synthesised in 1962,[11,12] is a synthetic, non-reducible or non-aromatisable AAS with the chemical name 17β-hydroxy-17α-methyl-2-oxa-5α-androstane-3-one. Structurally, oxandrolone is derived from testosterone, but possesses a novel chemical configuration. The Δ^4-3-oxo-group common to many AASs is absent in oxandrolone. Instead, it contains an oxygen atom in place of the methylene group at the 2 position and lacks a 4-ene function in the phenanthrene nucleus (A ring). The structural formula is shown in figure 1.

Oxandrolone belongs to the C17α-alkylated group of AASs. An alkyl group attached at the C17-α position of the steroid nucleus allows the AAS to be formulated as an oral preparation. Other AASs in this class include oxymetholone, stanozolol, methyltestosterone, metandienone (methandrostenolone), danazol, norethandrolone and fluoxymesterone.

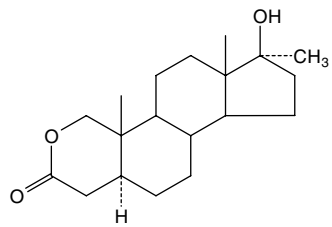

Fig. 1. Oxandrolone structure.

2.2 Pharmacokinetics

2.2.1 Absorption

Oxandrolone is well absorbed following oral administration, with peak serum concentrations occurring in approximately 1 hour. Plasma oxandrolone concentrations decline in a biphasic manner, with a distribution half-life (α-phase) of 30 minutes and an elimination half-life (β-phase) of approximately 9 hours.[13] Oxandrolone is 95% protein bound.

2.2.2 Metabolism

In marked contrast with other oral AASs that are metabolised extensively, oxandrolone is relatively resistant to liver biotransformation.[13,14] Approximately 28% of oxandrolone is excreted unchanged and unconjugated in the urine.[13,15] Metabolites of oxandrolone are 17-epioxandrolone and 16α- and 16β-hydroxyoxandrolone. The presence of an unusual δ-lactone group and lack of a 4-ene function in the A ring of oxandrolone may contribute to its greater stability against metabolic transformation. Hydroxylation is mostly suppressed during phase I metabolism,[13] and no glucuronidation occurs because of steric hindrance of the 17β–hydroxyl group with the glucuronic acid moiety in phase II transformation. Instead, oxandrolone is preferentially sulphated to 17-epioxandrolone. The lack of appreciable biotransformation and the high degree of protein binding result in oxandrolone having higher plasma levels than methyltestosterone.[11]

2.3 Pharmacodynamics – Anabolic and Androgenic Activity

Oxandrolone has marked anabolic activity and few androgenic effects.[11,16-19] In comparison with testosterone and methyltestosterone, oxandrolone has a high anabolic : androgenic ratio (10 : 1).[2]

The anabolic activity of oxandrolone in humans is approximately 6.3 times that of methyltestosterone (95% CI 3.8, 10.6) after oral doses.[11] Nitrogen balance studies conducted in patients recovering from episodes resulting in paraplegia or hemiplegia were used to calculate a steroid protein activity index (SPAI). The relative SPAI for oxandrolone and testosterone propionate were 2.8 and 1, respectively; the magnitude reflecting higher anabolic potency.[16]

In animal studies, oral oxandrolone had ≤24% of the androgenic activity of methyltestosterone[18] and was demonstrated to be of very low toxicity to mice and rats.[11]

It is suggested that the potency of oxandrolone can be attributed to its unique structure – an oxygen rather than a carbon atom at position 2 in the A ring.[11]

3. Clinical Efficacy of Oxandrolone

Oxandrolone has shown to be beneficial in patients requiring anabolic support and to promote beneficial clinical outcomes in catabolic conditions, including HIV-related muscle wasting, severe burn injury, trauma following major surgery, neuromuscular disorders, alcoholic hepatitis and chronic illness or muscle wasting of unclear aetiology. In the US, oxandrolone is the only AAS that is US FDA approved for restitution of weight loss after severe trauma, extensive surgery or chronic infections, malnutrition due to alcoholic cirrhosis, and Duchenne's or Becker's muscular dystrophy.

A Medline search (Ovid Web Gateway) of the medical literature with the subject heading oxandrolone and no language limitations, from January 1966 to February 2003 inclusive, was conducted. An examination of articles from bibliographies of review articles and source articles was also carried out. Abstracts were not used if a journal article was subsequently published.

Our review of the studies investigating the clinical efficacy of oxandrolone in catabolic disorders, and wasting associated with HIV infection, neuromuscular and miscellaneous disorders is summarised in the following sections and associated tables. Statistically significant improvements were collated in the areas of body composition, recovery, muscle strength and function, and/or functional status. Values shown are absolute changes or expressed as a percentage improvement from baseline measures or a percentage improvement above that of a control group, if present. Oxandrolone is also used in the treatment of short stature due to Turner's

syndrome and constitutional delay of growth and puberty. These conditions do not fall into the scope of this review and, thus, are not discussed.

Of the 43 studies available for review, 44% were randomised, controlled studies, 35% time series, 14% case reports, 5% retrospective reviews and 2% prospective descriptive reviews. The number of patients totalled 1859, and was comprised of 85% males and 15% females in the 75% of studies reporting gender. The average age in the studies ranged from 7 to 81 years. The mean duration of participants of oxandrolone treatment was 4.5 months (range 0.75–12 months). Oxandrolone was given orally, most often in dosages of 5–20 mg/day but up to 80 mg/day for patients with moderate to severe alcoholic hepatitis.

3.1 Catabolic Disorders

The largest number of patients studied have been those with catabolic illnesses, such as alcoholic liver disease and burn injury.[20-33] Most of these studies, presented in table I and table II, are robustly designed, randomised controlled trials featuring short durations of oxandrolone treatment. All of them report statistically significant and clinically meaningful improvements in body composition, recovery from injury/illness and/or survival in treated patients relative to controls. Little or no toxicity is reported in association with oxandrolone in these study groups, other than transient, mild elevation of liver enzyme levels in some studies (see section 4.2).

3.1.1 Acute Catabolic Disorders

Severe burn injury leads to an acute catabolic state, characterised by rapid, marked loss of lean muscle and visceral protein. The severity of complications correlates with the loss of body protein and impacts on morbidity and mortality. Treatment with oxandrolone has been shown to attenuate the hypermetabolic response, to significantly enhance muscle protein synthesis by increasing the efficiency of intracellular amino acid utilisation, decrease weight loss and net nitrogen loss, increase body mass and physical function, improve healing time, decrease complications and improve mortality and outcome (table I).

3.1.2 Chronic Catabolic Disorders

Patients with alcoholic hepatitis showed improvements in body composition, liver function, survival rate and malnutrition with oxandrolone administration (table II). No randomised, controlled trials have yet been carried out in chronic lung disease, although similar benefits are suggested in the uncontrolled studies with regard to body composition and functional status. There is a need for well designed studies in this cohort, in particular comparisons of oxandrolone and alternative methods of promoting anabolism in chronic obstructive pulmonary disease (COPD) such as protein/energy nutritional supplementation, anabolic exercise or multifaceted pulmonary rehabilitation programmes.

3.2 HIV/AIDS-Associated Wasting

Studies of patients with HIV/AIDS (table III) comprise the next largest category of clinical trials of oxandrolone.[38-48] Most of these studies are small in size, not all have a robust randomised, controlled trial design, and few women are represented, as might be expected. However, all of the studies report positive clinical outcomes for HIV-associated wasting, which are generally statistically significant, in the areas of body composition, muscle function or nutritional status. The well designed study by Berger et al.[48] is most promising, reporting significant improvements in bodyweight, appetite and physical activity levels in men with HIV infection taking oxandrolone 15 mg/day over 4 months.

Three of the studies[41,42,44] combined oxandrolone with progressive resistance training and documented benefits of the combined treatment. Although not significant, the results of Romeyn and Gunn[41] indicate a trend towards greater gains with combined treatment than oxandrolone alone. Strawford et al.[42] found that combined drug and progressive resistance training provided significantly greater improvements to bodyweight, nitrogen retention, lean body mass and bone mineral content, as well as reduced fat mass, compared with training alone. Additionally, upper and lower body muscle strength and function were significantly enhanced. Pharo et al.[44] demonstrated a significant dose-

Table I. Efficacy and adverse effects of oxandrolone (OX) in acute catabolic disorders

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
Burn injury						
Demling & DeSanti[33] (2003)	50 (M & F) [70y]	Randomised, controlled study	Until discharge or transfer to rehabilitation (20 mg/day)	Body composition: ↓ weight loss (4.5% less weight loss with OX) ↓ nitrogen loss (5 g/day less with OX) Recovery: ↓ time to heal standard donor site (30% less with OX) ↓ length of hospital stay (in days per % surface burn; OX 35% < control and OX 56% < predicted)	<0.05 <0.05 <0.05	Hepatic dysfunction (transient, mild ↑ AST, ALT): OX 20% (control 25%) Androgenic effects: 0% Cholesterol changes: 0% Behavioural changes: 0%
Demling & DeSanti[25] (2001)	22 (M & F) [35y]	Randomised, controlled study	3–4wk (20 mg/day)	Body composition: 50% less weight loss with OX Recovery: faster healing (7–8 days less with OX)	<0.05 <0.05	Hepatic dysfunction: 0% Androgenic effects: 0% Cholesterol changes: NR Behavioural changes: 0%
Hart et al.[28] (2001)	14 (7M, 7F) [8y]	Time series, prospective, cohort, analytic study (uncontrolled)	5mo (0.1 mg/kg bid for 5 days)	Muscle metabolism: ↑ muscle protein net balance ↑ muscle protein synthesis (104% greater with OX) ↑ protein synthesis efficiency (18.6% greater with OX)	<0.05 <0.05 <0.05	Hepatic dysfunction: 0% Androgenic effects: 0% Cholesterol changes: NR Behavioural changes: 0%
Demling & DeSanti[26] (2001)	25 (M & F) [34y]; 15 (M & F) [60y]	Randomised, controlled study	≥1mo (10mg bid)	Body composition: ↑ bodyweight (4kg greater increase with OX) ↑ % LBM of weight gain (22% greater with OX) Functional status: ↑ functional independence measures (12–19% better with OX) Recovery: ↓ length of stay (8 days less with OX)	<0.05 <0.05 <0.05 <0.05	Hepatic dysfunction (transient ↑ AP of <50%): 14% Androgenic effects: 0% Cholesterol changes: NR Behavioural changes: 0%
Demling & Orgill[27] (2000)	20 (M & F) [47y]	Randomised, double-blind, placebo-controlled study	29 days (20 mg/day)	Body composition: ↓ weight loss (5kg less with OX) ↓ less net nitrogen loss (9 g/day less with OX) Recovery: faster healing time (4 days less with OX)	<0.05 <0.05 <0.05	Hepatic dysfunction: 0% Androgenic effects: 0% Cholesterol changes: NR Behavioural changes: NR
Morton et al.[29] (2000)	1 (M) [31y]	Case report[a]	2.5mo (10mg bid for 7.5wk; 10mg daily for 2.5wk)			Hepatic dysfunction: NR Androgenic effects: NR Cholesterol changes: NR

Continued next page

Table I. Contd

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
						Behavioural changes:[a] persistent, disruptive, aggressive behaviour; mood lability, agitation, irritability; symptoms subsided on withdrawal of drug
Demling[30] (1999)	60 (33M, 27F) [46y]	Randomised, controlled study	1mo (20 mg/day)	Body composition:		Hepatic dysfunction: 0%
				↓ weight loss (5kg less with OX)	<0.05	Androgenic effects: 0%
				↓ net nitrogen loss (8 g/day less with OX)	<0.05	Cholesterol changes: NR
				Recovery:		Behavioural changes: NR
				faster healing time (4 days less with OX)	<0.05	
Aleem et al.[32] (1999)	49 (35M, 14F) [42y]	Retrospective review of patients with OX and no OX	Until discharge or wounds ≤5% open (10mg bid)	Recovery:		Hepatic dysfunction: NR
				↓ length of stay per % TBSA burn grafted (0.5% shorter with OX)	NR	Androgenic effects: NR
						Cholesterol changes: NR
				↓ need for inpatient rehabilitation	NR	Behavioural changes: NR
				↓ infection rates	NR	
Demling & DeSanti[31] (1997)	25 (M & F) [36y]	Randomised, controlled study	3wk (10mg bid)	Body composition:		Hepatic dysfunction: 0%
				↑ bodyweight (4.5kg greater increase with OX)	<0.05	Androgenic effects: 0%
				Functional status:		Cholesterol changes: NR
				↑ physical therapy index (26% better with OX)	<0.05	Behavioural changes: 0%
				Recovery:		
				faster discharge time (13 days sooner with OX)	<0.05	
Acute multiple trauma						
Gervascio et al.[34] (2000)	60 (55M, 5F) [34y]	Randomised, double-blind, placebo-controlled study	1mo (10mg bid)	Body composition (on BIA):		Hepatic dysfunction: 0%
				↓ body cell mass (1.6kg less of a decrease with OX)	>0.05	Androgenic effects: NR
						Cholesterol changes: NR
				Recovery:	<0.05	Behavioural changes: NR
				↑ prealbumin levels (7 mg/dL higher in OX group)		
				↑ length of stay (3 days longer with OX)	>0.05	
				↑ length of ICU stay (2 days longer with OX)	>0.05	
				↑ frequency of pneumonia or sepsis (total of 5 more episodes occurred in the OX group than in the placebo group)	>0.05	

a Patient displayed complications of pneumonia and pharmacologically induced and burn injury delirium. He also had a history of premorbid mania, family violence, childhood abuse and personality disorder.

ALT = alanine transaminase; **AP** = alkaline phosphatase; **AST** = aspartate transaminase; **BIA** = bioelectric impedance analysis; **bid** = twice daily; **F** = female; **ICU** = intensive care unit; **LBM** = lean body mass; **M** = male; **mo** = months; **NR** = not reported; **TBSA** = total body surface area; **wk** = weeks; **y** = years; ↑ indicates increased; ↓ indicates decreased.

Table II. Efficacy and adverse effects of oxandrolone (OX) in chronic catabolic disorders

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise stated)	p-Value	Adverse effects (% of OX recipients)
Moderate to severe alcoholic hepatitis						
Mendenhall et al.[20] (1995)	271 (M & F) [50y]	Randomised, double-blind, placebo-controlled study	3mo (80 mg/day for 1mo; 40 mg/day for 2mo)	Body composition: ↑ mid arm muscle area (4.2 mm^2 greater increase with OX) ↑ creatinine height index (15.8% greater increase with OX) ↑ % ideal bodyweight (5.8% better with OX)	 0.02 0.03 0.04	Hepatic dysfunction: NR Androgenic effects: NR Cholesterol changes: NR Behavioural changes: NR
Mendenhall et al.[21] (1993)	273 (M) [50y]	Randomised, double-blind, placebo-controlled study	3mo (80 mg/day for 1mo; 40 mg/day for 2mo)	Recovery in patients with moderate (but not severe) malnutrition: ↑ survival at 6mo (17% greater with OX) ↓ severity of liver injury (20% less with OX) ↓ malnutrition (19% less with OX) Only OX plus adequate caloric intake improved mortality (by 14%)	 0.037 0.03 0.05 0.002	Hepatic dysfunction: 0% Androgenic effects: 0% Cholesterol changes: NR Behavioural changes: NR
Bonkovsky et al.[22,23] (1991)	39 (19M, 20F) [42y]	Randomised, controlled study	3wk (20mg qid)	Body composition: improved visceral protein ↑ serum albumin levels greater ↑ prealbumin levels (increase in levels in OX group 70% greater) greater serum transferrin levels (serum transferrin levels 40% higher in OX group) Recovery: improved liver function ↑ antipyrine metabolism rate (375 mL/min per 1000mL liver higher in the OX group) ↑ bilirubin levels ↓ serum AST levels	 <0.00001 <0.05 <0.05 <0.025 <0.00001 <0.00001	Hepatic dysfunction (transient ↑ AST of ≤50 IU/L): <20% Androgenic effects: 0% Cholesterol changes: NR Behavioural changes: 0%
Mendenhall et al.[24] (1984)	263 (M) [51y]	Randomised, controlled study	1mo (80 mg/day)	Recovery: ↑ survival at 6mo (16% greater with OX) ↑ α-fetoprotein levels at 1mo (279% higher in OX group) – may reflect cell replication and	 0.02 0.03	Hepatic dysfunction: 0% Androgenic effects: NR Cholesterol changes: NR Behavioural changes: NR

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Table II. Contd

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise stated)	p-Value	Adverse effects (% of OX recipients)
				regeneration		
				↓ rehospitalisation (rate 8.4% less with OX)	NR	
Chronic obstructive pulmonary disease						
Yeh et al.[35] (2002)	128 (57M, 71F) [69y]	Time series, (multicentre) prospective open-label, uncontrolled clinical trial	4mo (10mg bid)	Body composition:		18% discontinued OX
				↑ bodyweight in 84% of OX patients (mean increase 2.1kg vs baseline)	<0.05	Hepatic dysfunction (↑ transaminase levels): 11.5%
				↑ body cell mass (on BIA) [+1.4kg vs baseline]	<0.05	(transient in 4.6%, treatment
				↑ fat mass (on BIA) [+0.5kg vs baseline]	>0.05	discontinued in 6.9%)
				Functional status:		Androgenic effects: 12% of
				↑ Karnofsky performance score	0.02	women (alopecia, hirsutism,
				↓ respiratory medication use (−15% vs baseline)	<0.05	deepened voice,
				↑ 6 min walk distance (+11m vs baseline)	>0.05	clitoromegaly)
				↑ appetite score (0.75 improvement vs baseline)	0.07	Cholesterol changes: 0%
						Behavioural changes: 0%
						Other: oedema (7%)
Bowen et al.[36] (1998)	17 (M & F) [mean age not given]	Time series, open-label, uncontrolled	2mo (0.2 mg/kg/day)	Body composition:		Hepatic dysfunction: 0%
				↑ % body fat (+2.8% vs baseline)	0.001	Androgenic effects: NR
				Muscle strength:		Cholesterol changes: 0%
				↑ leg extension strength (+32% vs baseline)	0.001	Behavioural changes: NR
				Functional status:		
				↑ VO_{2max} (+14% vs baseline)	0.001	
				↑ FEV_1 (+0.05 L/min vs baseline)	NR	
Crohn's disease						
Kravetz et al.[37] (1997)	1 (F) [29y]	Case report	3.5mo (7.5mg bid for 1mo; 10mg bid for 2.5mo)	Body composition (on BIA):		Hepatic dysfunction: NR
				↑ bodyweight (+10.7kg vs baseline)	NR	Androgenic effects: facial
				↑ body cell mass (+2.4kg vs baseline)	NR	hair at 3.5mo (discontinued
				↑ fat mass (+10.1kg vs baseline)	NR	OX)
				↑ bodyweight (at 1y after discontinuation: 19.3kg increase vs baseline)	NR	Cholesterol changes: NR
						Behavioural changes: NR

AST = aspartate transaminase; **BIA** = bioelectric impedance analysis; **bid** = twice daily; **F** = female; **FEV_1** = forced expiratory volume in 1 second; **M** = male; **min** = minute; **mo** = months; **NR** = not reported; **qid** = 4 times daily; **VO_{2max}** = maximum oxygen consumption; **wk** = weeks; **y** = years; ↑ indicates increased; ↓ indicates decreased.

Table III. Efficacy and adverse effects of oxandrolone (OX) in wasting associated with HIV/AIDS

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
Earthman et al.[39] (2002)	25 (15 AIDS, 10 HIV-positive; 24M, 1F) [41y]	Prospective, descriptive study, uncontrolled, open-label	18.6wk [mean] (20 mg/day)	Body composition: ↑ bodyweight (+2.6kg vs baseline) ↑ BCM (on deuterium dilution) [+3.6kg vs baseline] ↑ LTM (on DEXA) [+3kg vs baseline] ↓ truncal adiposity in HIV-positive group only ↓ total fat mass (on DEXA) [−1.7kg vs baseline] ↓ truncal fat mass (on DEXA) [−1.1kg vs baseline] Functional outcome: ↑ quality of life (on FAHI) ↑ appetite (on FAACT)	 <0.0001 <0.0001 <0.0001 0.05 0.03 0.056 0.032	Hepatic dysfunction (↑ transaminase levels): 6% (3% discontinued OX, 3% withdrew from study) Androgenic effects: 3% (acne – withdrew from study) Cholesterol changes: 0% Behavioural changes: 3% (anxiety – OX dose reduced)
Cioroiu & Hanan[38] (2001)	1 (M) [57y]	Case report	2mo (20 mg/day)	Recovery: chronic venous stasis ulcer present for 8y (wound area 580 mm^2) healed within 3mo and remained healed		Hepatic dysfunction: NR Androgenic effects: NR Cholesterol changes: NR Behavioural changes: NR
Romeyn & Gunn[41] (2000)	13 (12M, 1F) [mean age not given]	Randomised, controlled study	3mo (10mg bid [n = 6]; 10mg bid + PRT [n = 7])	Body composition: ↑ bodyweight (on BIA) vs baseline OX: +1.1kg (1.9%); OX + PRT: +2kg (3.2%) at 1mo OX: + 2.7kg (4.6%); OX + PRT: +3.9kg (5.6%) at 3mo	 >0.05 (for OX and OX + PRT) >0.05 (for OX and OX + PRT)	Hepatic dysfunction: NR Androgenic effects: NR Cholesterol changes: NR Behavioural changes: NR
Fox-Wheeler et al.[40] (1999)	9 (5M, 4F) [10y]	Time series, open-label, uncontrolled	3mo (0.1 mg/kg/day)	Body composition and anthropometrics: ↑ bodyweight (+1.2kg vs baseline) ↑ BMI (+0.51 kg/m^2 vs baseline) ↑ height (+1.3cm vs baseline) ↑ arm muscle area (+25.8 cm^2 vs baseline) ↑ muscle (on CT of humerus)	 0.002 0.02 0.02 0.02 0.05	Hepatic dysfunction: 0% Androgenic effects: 0% Cholesterol changes: NR Behavioural changes: 0%

Continued next page

Table III. Contd

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
				↓ tricep skinfold (−0.75mm vs baseline)	0.05	
				↓ fat stores (on CT)	>0.05	
				↑ femoral cortical bone area (on CT)	0.02	
				↑ femoral cortical bone cross sectional area (on CT)	0.02	
				↑ prealbumin levels	0.002	
Strawford et al.[42] (1999)	22 (M) Eugonadal [40y]	Randomised, double-blind, placebo-controlled study	2mo (20 mg/day + PRT [n = 11]; PRT alone (placebo; n = 11)	Body composition (on DEXA vs control):		Hepatic dysfunction (↑ transaminase levels): 18% (transient in 9%, OX discontinued in 9%) Androgenic effects (increased libido): 15% OX, 15% PL Cholesterol changes: % NR (↓ HDL by 36% p < 0.001) Behavioural changes: 81% (mood swings [45% OX, 25% PL], anxiety [36% OX])
				↑ bodyweight: 2.5kg greater with OX	0.03	
				↑ nitrogen retention: 1.8kg greater with OX	0.05	
				↑ LBM: 3.1kg greater with OX	0.005	
				↓ fat mass: 0.1kg greater with OX	0.005	
				↑ BCM: 25g greater with OX	<0.001	
				↑ resting energy expenditure (+836kJ greater with OX)	0.03	
				Muscle function:		
				↑ upper and lower body muscle strength (1RM)	0.02–0.05	
				↑ shoulder and knee strength (extension, flexion by Cybex dynamometry)	0.01–0.04	
Fisher et al.[43] (1998)	26 (M) [mean age not given]	Time series, open-label, uncontrolled	12mo (20 mg/day)	Body composition (on BIA):		Hepatic dysfunction: 0% Androgenic effects: 0% Cholesterol changes: 0% Behavioural changes: 0%
				↑ bodyweight (+5.2kg vs baseline)	<0.01	
				↑ BCM (+3.5kg vs baseline)	<0.05	
				Functional status:	<0.01	
				↑ appetite (at 2 and 4mo)	<0.05	
				↑ sense of well-being (at 2mo)		
Poles et al.[45] (1997)	21 (20M, 1F) [38y]	Time series, open-label, uncontrolled	12mo (20 mg/day)	Body composition (on BIA):		Hepatic dysfunction: 0% Androgenic effects: 0% Cholesterol changes: 0% Behavioural changes: 0%
				↑ bodyweight (+9.1kg vs baseline)	0.022	
				↑ BCM (+5.4kg vs baseline)	0.002	
				↑ Body fat (+3kg at 6mo; +2.2kg at 12mo)	0.006 (6mo); 0.171 (12mo)	
				↑ intracellular water (+5.2L vs baseline)	0.002	
Pharo et	20 (F) [mean	Randomised study	4mo (10 or 20	Body composition (on BIA):		Hepatic dysfunction: 0%

Continued next page

Table III. Contd

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
al.[44] (1997)	age not given]		mg/day) [OX + PRT]	↑ bodyweight (+3.2kg vs baseline) after 7wk	NR	Androgenic effects: 0%
				Functional status:	NR	Cholesterol changes: NR
				improved quality of life (by 50%) after 7wk		Behavioural changes: 0%
Salvato et	29 (M & F)	Retrospective	Average 9mo	Body composition:		Hepatic dysfunction: 0%
al.[46] (1997)	[mean age not	chart review,	[4–18mo] (OX	↑ bodyweight (+4kg vs baseline)		Androgenic effects: NR
	given]	noncomparative of	[n = 9], ND + TC	↑ albumin levels (+15.1% vs baseline)	NR	Cholesterol changes: NR
		HIV/AIDS patients	[n = 7], OX +	Functional status:		Behavioural changes: NR
		on AAS treatment	ND + TC [n =	↑ quality of life (148% improvement vs baseline)	NR	
			13]; dosages not	↑ CD4+ cell count (+197% vs baseline)	NR	
			provided)	↓ HIV viral load (−11.8% vs baseline)	NR	
Fisher &	16 (M) [mean	Time series, open-	1mo (20 mg/day	Body composition (on BIA):		Hepatic dysfunction: 0%
Abbaticola[47]	age not given]	label, uncontrolled	+ l-glutamine 20	↑ bodyweight (+2.9kg vs baseline)	0.0001	Androgenic effects: 0%
(1997)			g/day)	↑ BCM (+1.2kg vs baseline)	0.0001	Cholesterol changes: 0%
				↑ body fat (+0.7kg vs baseline)	>0.05	Behavioural changes: 0%
Berger et	63 (M) [40y]	Multicentre,	4mo (5 or 15	Body composition:		Hepatic dysfunction: 0%
al.[48] (1996)		randomised,	mg/day)	15mg group: continual weight gain (maximum	0.009–	Androgenic effects: 0%
		double-blind,		1.8kg)	0.011	Cholesterol changes: 0%
		placebo-controlled		5mg group: maintained weight	>0.05	Behavioural changes: 0%
		study		Functional status (15mg group only):		
				↑ appetite	0.048	
				↑ physical activity	0.009	
				↓ CD4+ cell count (−5.8% vs baseline)	0.022	

AAS = anabolic androgenic steroid; **BCM** = body cell mass; **BIA** = bioelectric impedance analysis; **bid** = twice daily; **BMI** = body mass index; **CD4** = helper T cells; **CT** = computerised tomography; **DEXA** = dual x-ray absorptiometry; **F** = female; **FAACT** = Functional Assessment of Anorexia/Cachexia Therapy; **FAHI** = Functional Assessment of Human Immunodeficiency Virus Infection; **HDL** = high density lipoprotein; **LBM** = lean body mass; **LTM** = lean soft tissue mass; **M** = male; **mo** = months; **ND** = nandrolone decanoate; **NR** = not reported; **PL** = placebo; **PRT** = progressive resistance training; **RM** = repetition maximum; **TC** = testosterone cypionate; **wk** = weeks; **y** = years; ↑ indicates increased; ↓ indicates decreased.

response relationship in bodyweight and quality of life with oxandrolone and progressive resistance training.

3.3 Neuromuscular Disorders

Neuromuscular disorders, represented in table IV, also appear to respond well to oxandrolone treatment, with significant clinical benefits observed in all reported studies. Although several of these studies are small in size and uncontrolled, the randomised trials by Fenichel et al.[49] and Rutkove et al.[50] substantiate the findings in the uncontrolled studies. Improvements in body composition, muscle function, functional limitations, pulmonary function and wound healing were noted with oxandrolone treatment in the neuromuscular disease cohorts.

3.4 Miscellaneous Disorders

A final eight studies (table V), including two randomised trials, represent a heterogeneous grouping of clinical indications such as obesity, dyslipidaemia, and chronic psychiatric and medical diseases in the elderly. One of the earliest studies of oxandrolone with the longest duration of treatment is that of Gerondache et al.[12] in 1967, who found that older adults had improved appetite and nitrogen retention when receiving oxandrolone compared with placebo over a 12-month period.

4. Toxicity of AASs and Oxandrolone

Although few significant adverse effects were reported in the studies reviewed, oxandrolone has the potential to exhibit many of the adverse effects associated with AASs. These effects can be wide ranging and evident in the blood, cardiovascular, central nervous, musculoskeletal, gastrointestinal, renal, reproductive/endocrine and dermatological systems, as well as manifesting as psychological and behavioural effects. Detailed descriptions of these adverse effects can be gained from a number of reviews.[8,63-68] However, this review explores in detail the effects of oxandrolone and the C17α–alkylated AASs on the liver.

4.1 Adverse Hepatic Effects of AASs

Hepatotoxic effects are characteristically produced by AASs with an alkyl group attached at the C17-α position of the steroid nucleus.[69,70] Hepatic dysfunction is less frequently observed in AASs not containing the C17α-alkylated group. Adverse effects range from elevated liver enzymes and cholestatic jaundice to the more severe hepatic complications of peliosis hepatis, hyperplasia, adenomas and hepatocellular carcinoma.[69-72] Adenomas and carcinomas are known to regress following drug withdrawal.[73]

These adverse effects have mainly occurred with high dosages, prolonged use (>1 year), multiple concurrent anabolic agents and/or in the treatment of aplastic anaemia or Fanconi's anaemia.[70-72] The rate of development and severity of adverse effects is considered to be dose dependent[74] and therapeutic dosages of AAS rarely lead to serious hepatic dysfunction. A long-term study of patients treated with stanozolol or danazol showed no harmful hepatic effects over 15–47 months.[1] The reasons for hepatotoxicity of this group of drugs are unknown, but toxicity could be influenced by the patient's previous liver function status.[75]

Adverse hepatotoxic effects are predominantly ascribed to the other C17α-alkylated AASs rather than oxandrolone. No evidence exists to suggest that distinct, short-term treatment (≤3 months) with oxandrolone has led to the development of the more serious forms of hepatotoxicity. In addition, no specific cases of severe events have been attributed singularly to oxandrolone.

Elevated liver enzyme levels, including transient increases in bromosulfophthalein retention and concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin and alkaline phosphatase, have been reported during oxandrolone therapy. These effects have been noted to occur particularly after high dosages and/or administration for prolonged periods, but return to normal values on withdrawal of the drug.[11,27,51,53,62,72,76,77] Oxandrolone is widely used in the treatment of Turner's syndrome and constitutional delay of growth and puberty, with few significant adverse

Table IV. Efficacy and adverse effects of oxandrolone (OX) in neuromuscular disorders

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
Amyotrophic lateral sclerosis						
Rosenfeld et al.[51] (2000)	10 (7M, 3F) [52y]	Time series, open-label, uncontrolled	12mo (10mg bid)	Body composition: ↓ weight (−2.6% vs baseline) Muscle function: ↑ isometric muscle strength in 100% of patients Functional status: stabilised or ↑ FVC in 70% of patients	 NR NR NR	Hepatic dysfunction (elevated transaminase levels): 20% (transient in 10%, OX dosage reduction in 10%) Androgenic effects: 0% Cholesterol changes: NR Behavioural changes: 0%
Duchenne's muscular dystrophy						
Fenichel et al.[49] (2001)	31 (M) [7y]	Randomised, double-blind, placebo-controlled study	6mo (0.1 mg/kg/day)	Body composition: ↑ bodyweight (1.6kg greater with OX) ↑ height (1.6cm greater with OX) Muscle function: ↑ manual muscle strength ↑ 4 quantitative muscle tests (mean change from baseline for averaged scores: OX +0.784, PL −2.933) ↑ arm muscle strength Functional status: improved timed climbing, running, standing tests	 0.0004 0.007 0.13 0.02 0.005 >0.05	Hepatic dysfunction: 0% Androgenic effects: 0% Cholesterol changes: % NR (↓ HDL by 13U) Behavioural changes: 0%
Fenichel et al.[52] (1997)	10 (M) [7y]	Time series, open-label, uncontrolled	3mo (0.1 mg/kg/day)	Muscle function: ↑ average muscle strength (+0.315 vs baseline for average muscle score of 34 muscles)	 <0.01	Hepatic dysfunction: 0% Androgenic effects: 0% Cholesterol changes: NR Behavioural changes: 20% (transient aggression at 1mo only)
Inclusion body myositis						
Rutkove et al.[50] (2002)	16 (14M, 2F) [68.5y]	Randomised, double-blind,	3mo (10mg bid)	Body composition: ↑ LBM (by skinfolds) [1.7% greater with OX]	 0.014	Hepatic dysfunction: % NR (↑ ALT [7.5 IU/L]: p = 0.034;

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Table IV. Contd

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
		placebo-controlled, crossover study; 2–4mo OX washout		Muscle strength: ↑ upper body isometric strength (3.8kg more with OX) ↑ whole body isometric strength (9.4kg more with OX) Functional status: ↑ stair climb (+1 step/15s with OX)	 0.0063 0.06 <0.001	↑ AST [6 IU/L]: p < 0.001) Androgenic effects: 6% (mild acne [gender NR]) Cholesterol changes: % NR (↓ HDL [21.5 mg/dL]: p < 0.001; ↑ LDL [48.5 mg/dL]: p = 0.011) Behavioural changes: NR
Spinal cord injury						
Spungen et al.[53] (2001)	9 (M) [50y]	Case reports	1–12mo [mean 4mo] (20 mg/day)	Body composition: ↑ bodyweight (+4.5–13kg vs baseline) in 83% of patients Recovery: complete healing of previous non-healing pressure ulcers in 89% of patients	 NR NR	Hepatic dysfunction (transient ↑ ALT, AST): 33% (p > 0.05) Androgenic effects: NR Cholesterol changes: 66% (11% ↑ cholesterol above normal; 11% ↑ LDL above normal; 44% ↓ HDL below normal) Behavioural changes: NR
Spungen et al.[54] (1999)	10 (M) [41y]	Time series, open-label, uncontrolled	1mo (20 mg/day)	Body composition: ↑ bodyweight (+1.4kg, 2.2% vs baseline) Functional status: improved combined spirometric measures: (+9% vs baseline) FVC (+7.8%), FEV_1 (+7.5%), $FEF_{25–75}$ (+10%), FIVC (+8.5%), PEF (+10%) improved maximal inspiratory pressure: (+10% vs baseline) improved maximal expiratory pressure: (+9% vs baseline)	 0.01 <0.005 <0.005–0.05 <0.001 >0.05	Hepatic dysfunction: % NR (↑ ALT 200% above normal: p < 0.05) Androgenic effects: NR Cholesterol changes: % NR (↓ HDL by 47%: p < 0.0001) Behavioural changes: NR

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Table IV. Contd

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
				↓ Borg scale resting dyspnoea (−0.05 [−37%] vs baseline)	<0.05	
Demling & DeSanti[55] (1998)	8 (7M, 1F) [50y], 80% SCI	Time series, open-label, uncontrolled	4mo (20 mg/day)	Body composition:		Hepatic dysfunction: NR
				↑ bodyweight (16.7kg vs baseline)	<0.05	Androgenic effects: 0%
				Recovery of previously non-healing wounds:		Cholesterol changes: NR
				↑ wound healing rate by 4wk	<0.05	Behavioural changes: NR
				62.5% wounds healed completely		
				37.5% wounds healed by 75%		
				healing correlated with weight restoration (r = 0.67)	<0.05	

ALT = alanine transaminase; **AST** = aspartate transaminase; **bid** = twice daily; **F** = female; **FEF_{25-75}** = mean forced expiratory flow from 25–50% of the FVC; **FEV_1** = forced expiratory volume in 1 second; **FIVC** = forced inspiratory vital capacity; **FVC** = forced vital capacity; **HDL** = high density lipoprotein; **LBM** = lean body mass; **LDL** = low density lipoprotein; **M** = male; **mo** = months; **NR** = not reported; **PEF** = peak expiratory flow; **PL** = placebo; **r** = correlation coefficient; **s** = second; **SCI** = spinal cord injured; **wk** = weeks; **y** = years; ↑ = increased; ↓ = decreased.

events documented.[78] Some increases in liver function enzyme levels have been observed occasionally with the use of relatively low dosages (0.1–0.2 mg/kg/day).[19,60,78] Serum levels of aminotransferases or alkaline phosphatase were elevated in 3 of 32 girls with Turner's syndrome treated with oxandrolone 0.125 mg/kg/day for up to 2 years.[78] Suspected hepatic injury with oxandrolone usually occurs in a cholestatic pattern, with a <5-fold increase in AST and ALT levels, and a <3-fold increase in alkaline phosphatase levels, even when bilirubin levels are high.[71]

Reports of AAS-induced hepatic dysfunction have been based on elevated levels of ALT and AST rather than liver biopsy data.[1,79] Dickerman et al.[80] emphasise that elevated transaminase levels may be a result of muscle damage from intense resistance training, rather than liver damage. Thus, reports of hepatotoxicity from C17-α alkylated AASs based solely on increased AST and ALT levels may be overestimated. Moreover, the fear of hepatotoxicity may thwart potentially beneficial clinical investigations with these AASs.[80]

Jaundice, generally the main manifestation of AAS use, can develop 2–5 months after ingestion, and is related to individual susceptibility. Pre-existing liver disease will increase the risk of hepatic dysfunction.[74] AAS-induced hepatic injury displays a different histological pattern from that of injury caused by other drugs. Usually, complete recovery from AAS-induced jaundice and hepatic dysfunction occurs on withdrawal of the drug,[71] and does not recur with continued treatment.[73] Jaundice has been reported with use of stanozolol.[81]

AAS-induced cholestatic hepatitis exhibits a distinct histological difference from that caused by other drugs, such as chlorpromazine and erythromycin. Canalicular jaundice, normal parenchyma and the relative absence of portal inflammation are evident rather than the hepatocanalicular jaundice seen with other agents. Cholestatic hepatitis has been noted in patients treated with fluoxymesterone,[82] danazol,[83-85] methyltestosterone[86] and stanozolol.[87]

Interestingly, 3 weeks of therapy with high dosages of oxandrolone 80 mg/day did not exacerbate liver function abnormalities or cholestasis in patients with alcoholic hepatitis.[22] Dosages up to 200 mg/day for 14–108 days caused no renal or hepatic toxicity in women with metastatic carcinoma.[88]

Peliosis hepatis is a vascular lesion that consists of blood-filled cysts. C17α-alkylated AASs have been implicated in around 60 cases.[79] The pathogenesis of the lesion is unknown but may be separate from the hepatic dysfunction caused by these steroids. However, Paradinas et al.[89] proposed that a single mechanism might be responsible for cholestasis and peliosis hepatis. During hepatocyte hyperplasia, enlarged hepatocytes impinge on and occlude the hepatic veins, leading to blocked bile canaliculi and thus producing cholestasis, peliotic sinusoids and, possibly, oesophageal varices.

Peliosis hepatis has been associated with fluoxymesterone,[90,91] oxymetholone,[90,92-95] danazol,[96] metandienone (methandrostenolone)[97] and methyltestosterone[90] use. In an extensive review to 1984, 24 cases of peliosis hepatis associated with AAS administration for longer than 6 months were found.[63] Most patients in the cases reported had malignancies or significant haematological disorders and were ill before androgen therapy.[80,92-94,98] There are no reports of oxandrolone-associated peliosis hepatis.

Both benign and malignant hyperplasias and neoplasms have been reported with C17α-alkylated AAS administration.[74] These include diffuse hyperplasia, nodular regenerative hyperplasia, focal nodular hyperplasia, hepatocellular adenoma and hepatocellular carcinoma. The regression of lesions after drug withdrawal suggests a causative relationship between AASs and hyperplasias or neoplasms. Focal nodular hyperplasia was reported in an 11-year-old boy treated with oxandrolone 5 mg/day for 6 months for stunted growth.[99] The patient recovered following surgery. Furthermore, it was noted that the hyperplasia could have been coincidental; the tumour may have been caused by arterial malformation.[71]

Bleeding oesophageal varices attributed to nodular regenerative hyperplasia was observed in a 30-year-old bodybuilder taking oxandrolone 7.5mg plus other anabolic steroids over a period of 18 months. Although slight elevations in AST levels were reported, recovery was evident 6 months after discontinuation of AASs.[69] Nodular hyperplasia has characteristically been associated with oral contraceptives, but not AASs.[99]

Hepatic adenomas have been reported after danazol,[100,101] oxymetholone,[102,103] metandienone[104] and fluoxymesterone[82] administration. Three cases of death following primary adenoma have been reported in athletes taking AASs. Each had taken large doses of a number of agents over 3–5 years.[105-107] In the only two cases in which oxandrolone was implicated, one bodybuilder was also taking metandienone, stanozolol, metenolone and nandrolone decanoate for 4 years.[105] The other individual was also ingesting metenolone enanthate over 8 years.[108]

Hepatocellular carcinomas have been reported with use of oxymetholone,[94,109-113] fluoxymesterone,[90] and metandienone,[109] and occurrence is related to high dosages and long duration of therapy.[79] AAS-induced hepatocellular carcinoma appears to occur with higher frequency in men than women.[73] About 50% (48) of the AAS-associated tumours reported up to 1990 were diagnosed in patients with Fanconi's anaemia, a severe hereditary anaemia with a high incidence of malignant neoplasms; these patients may have been predisposed to hepatic tumour development.[73] Treatment was generally with oxymetholone.[114] Zimmerman and Ishak[74] report the onset of hepatocellular carcinoma at an average of 72 months after continued AAS administration, with an earlier onset in Fanconi's anaemia.

Friedl[73] suggested that the majority of AAS-associated tumours may not be evident until rupture. Moreover, he hypothesised that C17α-alkylated AASs produce no more tumours than the C17β-esterified steroids; rather, they are more readily detected through rupture. Some cases of severe hepatotoxicity have been noted after use of the C17β-

Table V. Efficacy and adverse effects of oxandrolone (OX) in miscellaneous disorders

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
Hereditary angioedema						
Barakat & Castaldo[56] (1999)	1 (F) [14y]	Case reports	12mo (7.5 mg/day)	Body composition:		Hepatic dysfunction: 0%
				weight gain disappeared	NR	Androgenic effects: 0%
				Functional status:		Cholesterol changes: NR
				better disease control	NR	Behavioural changes: 0%
				↓ frequency and severity of attacks	NR	
	1 (M) [38y] type 2		3mo (20 mg/day)	Functional status: no major attacks	NR	
Dyslipidaemia						
Lovejoy et al.[57] (1995)	30 obese (M) [48y]	Randomised, double-blind placebo-controlled study	9mo [OX for 3mo] (10 mg/day)	Body composition (on CT and DEXA):		Hepatic dysfunction: 0%
				↓ visceral fat area (35 cm^2 [7.3%] less with OX)	<0.05	Androgenic effects: NR
				↑ subcutaneous fat loss (24.6 cm^2 greater loss with OX)	<0.05	Cholesterol changes: % NR (↓ HDL [0.31 mmol/L], p > 0.05; ↑ LDL [0.68 mmol/L], p = 0.01)
				↑ thigh muscle area (9.19 cm^2 bigger with OX)	>0.05	
						Behavioural changes: NR
Malmendier et al.[58] (1978)	43 (37M, 6F) [49y]	Time series	12mo total (phases I–IV: 1mo PL; 3mo OX 7.5 mg/day; 1mo PL; 7mo OX 7.5 mg/day)	Body composition:		Hepatic dysfunction: 0%
				↑ bodyweight (4.5% more with OX) in type IV and V	<0.05	Androgenic effects: 0%
				Cholesterol changes:		Cholesterol changes: 42% (↑ 10% in type IV patients)
				↓ serum triglyceride levels in type III, IV, V hyperlipoproteinaemia (24–83% decrease with OX)	<0.05	Behavioural changes: 0%
				↓ pre-β lipoprotein levels (15–50% greater decrease with OX)	<0.05	
				↓ serum cholesterol in type III (25% greater decrease with OX)	<0.05	
Enholm et al.[59] (1975)	7 (M) [43y]	Time series, open-label, uncontrolled	3wk (7.5 mg/day)	↑ total postheparin lipolytic activity (+100% vs baseline) due to:	<0.05	Hepatic dysfunction (transient ↑ AST, ALT 2–52IU above normal): 100% (p < 0.05)
				↑ postheparin hepatic lipase activity (+167% vs baseline)	<0.001	
				↑ phospholipase A_1 activity (+134% vs baseline)	<0.05	Androgenic effects: NR

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Table V. Contd

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
						Cholesterol changes: 0%
						Behavioural changes: NR
Doyle et al.[60] (1974)	47 (42M, 5F) [55y]	Time series	12mo total (phases I–IV: 1mo PL; 3mo OX 7.5 mg/day; 1mo PL; 7mo OX 7.5 mg/day)	High rate of response in types III, IV and V hyperlipoproteinaemia (57%, 76% and 80%, respectively)		Hepatic dysfunction (small transient ↑ AST, ALT): 13%
						Androgenic effects: 0%
				Cholesterol changes:		Cholesterol changes: 0%
				↓ plasma triglycerides (36% vs placebo in 49% of patients)	<0.001	Behavioural changes: 0%
				↓ plasma cholesterol (−2% in 34% of patients)	>0.05	
Lipodermatosclerosis						
Segal et al.[61] (2000)	1 (F) [54y]	Case report	3mo (10mg bid)	Recovery:		Hepatic dysfunction: 0%
				reduction in pain score (from 7/10 to 3/10) in 2wk	NR	Androgenic effects: NR
				symptoms abated after 3mo sufficiently to discontinue OX		Cholesterol changes: NR
Mental disorder (unspecified) with systemic disease						
Sansoy et al.[62] (1971)	34 (25M, 9F) [61y]	Time series, open-label, uncontrolled	2mo (15–20 mg/day)	Body composition:		Hepatic dysfunction: 74% (↑ AST in 53%; ↑ BSP retention in 35%)
				↑ bodyweight (+4.2 kg vs baseline) in 82% of patients		
				↑ total serum protein in 41% of patients	0.01	Androgenic effects: NR
				Recovery:		Cholesterol changes: 0%
				disappearance of premature ventricular contractions in five patients		Behavioural changes: NR
				improvement in bony system of 50% of patients with osteomyelitis		
Elderly with arteriosclerosis and multiple chronic diseases						
Gerondache et al.[12] (1967)	24 (12M, 12F) [81.2y]	Randomised, crossover study	12mo (3mo OX 7.5 mg/day, 3mo PL, 3mo OX 7.5 mg/day, 3mo PL)	Body composition:		Hepatic dysfunction (transient): 67% (↑ AST in 17% [p = 0.001], ↑ BSP in 67% [p = 0.001])
				weight gain (0.5kg greater with OX)	>0.05	
				↓ serum cholesterol (10% greater decrease with OX)	0.01	
				↓ serum triglycerides (17% greater decrease	0.01	Androgenic effects: 0%

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Table V. Contd

Study (year)	No. of patients (gender) [mean age]	Study design	Study duration (dose)	Efficacy (OX vs control unless otherwise indicated)	p-Value	Adverse effects (% of OX recipients)
				with OX)		Cholesterol changes: 0%
				↓ total urinary nitrogen excretion (12% greater	0.05	Behavioural changes: NR
				decrease with OX)		Other: oedema (20%) in patients with CHF
				Functional status:	<0.05	
				improved appetite in 17% of patients		
				improved psychological test performance in 61% of		
				patients		

ALT = alanine transaminase; **AST** = aspartate transaminase; **bid** = twice daily; **BSP** = bromosulfophthalein; **CHF** = congestive heart failure; **CT** = computerised tomography; **DEXA** = dual x-ray absorptiometry; **F** = female; **HDL** = high density lipoprotein; **LDL** = low density lipoprotein; **M** = male; **mo** = months; **NR** = not reported; **PL** = placebo; **wk** = weeks; **y** = years; ↑ indicates increased; ↓ indicates decreased.

esterified steroids. Turani (1983, cited by Friedl[73]) described peliosis and tumours associated with C17β-esterified steroids that were found on post-mortem examination of patients with renal failure and anaemia, respectively. A case report described benign hepatic adenoma in a patient treated with testosterone enanthate for 11 years.[115]

Haupt and Rovere[63] reported in 1984 that benign and malignant tumours associated with AAS use are rare; finding 36 cases in a search of the literature. In all cases, AAS treatment had been for >24 months. Another five possible cases are accounted for up to 1989.[73] Furthermore, Basaria et al.,[1] after systematic review of the literature, failed to find any clear increase in the incidence of liver cancer associated with AAS use. AASs implicated in hepatocarcinomas were being taken for prolonged periods (1–7 years). Most anabolic steroid-associated hepatomas were isolated case reports and regressed after cessation of the drug.[73] Similarly, hepatocellular hyperplasia and hepatocellular adenomas occurred in patients taking high dosages or untraditional combinations of steroids.[1] No decisive studies show evidence of AAS-induced hepatocellular carcinomas with therapeutic doses.

4.2 Adverse Hepatic and Other Effects of Oxandrolone

A summary of the adverse events in studies investigating the clinical efficacy of oxandrolone is presented in table I, table II, table III, table IV and table V. For general androgenic effects, cholesterol changes and behavioural changes, the percentage of the treated individuals who were affected is reported when the incidence of the adverse effect was statistically or clinically significant. In the area of hepatic dysfunction, all adverse findings are stated.

Not all of the studies reported the full spectrum of possible adverse events attributable to oxandrolone, so it is not possible to state the precise prevalence of these toxicities. Adverse hepatic events were investigated in 36 (84%) of the 43 studies and 14 (39%) of these reported adverse hepatic events. Oxandrolone did not exhibit the more serious adverse hepatic effects of the C17α-alkylated AASs, as has

been reviewed in section 4.1. Most of the hepatic toxicity reported consisted of asymptomatic and reversible elevations of transaminases during or after completion of the study, without evidence of permanent hepatic damage. Three studies (7%) reported the need to discontinue oxandrolone treatment because of elevated transaminase levels.[35,39,42]

Androgenic effects were assessed in 27 of the 43 studies. Amongst the approximately 1000 patients in these 27 studies, androgenic adverse effects were reported in only 14 individuals (facial hair growth, acne, alopecia, deepened voice, increased libido, clitoromegaly). This low incidence was observed despite the fact that 30 of the 43 studies included women. Two studies documented withdrawal of female patients because of virilising effects.[35,37] The low incidence of androgenic adverse effects reported with oxandrolone attests to the more favourable ratio of anabolic : androgenic potency of the drug compared with many other AASs which have been used clinically. However, because only 15% of the patients in studies in which gender was reported were women, it would be important to study this drug further in larger numbers of women to substantiate its apparent tolerability in this regard.

Cholesterol alterations were reported in only 19 of the 43 clinical studies reviewed. Among these, adverse effects were noted in seven studies (37%). The predominant effect was to lower high density lipoprotein (HDL) cholesterol (six of seven studies) by 36–47% below baseline values, which is comparable with that seen with other AASs;[68] in addition, four studies reported elevations of total or low density lipoprotein cholesterol. The long-term consequences of such changes in cholesterol, such as arteriosclerosis, coronary heart and cerebrovascular disease, would not be evident in the studies conducted to date, which have been of relatively short duration. However, the potential therapeutic use of oxandrolone for chronic illnesses or age-related sarcopenia, as opposed to recovery from illness or trauma, makes this adverse effect an important consideration in risk-benefit analyses.

The only other adverse effects noted in these trials were psychological/behavioural changes in 13 patients,[29,42,52] and the oedema in elderly subjects; five with heart failure[12] and nine with COPD.[35]

As there are significantly more AR binding sites in the prostate than in muscle,[116] the risk of prostate cancer with use of AASs must be considered. No such cases have been reported with oxandrolone in the studies reviewed, but longer term follow-up is required.

It would be helpful if future studies followed standardised and rigourous reporting methods for all of the common adverse effects of this medication, so that a more complete profile of the prevalence of these adverse events can be compiled.

5. Potential Utility of Oxandrolone for the Treatment of Sarcopenia

An area of great potential for anabolic agents such as oxandrolone is that of sarcopenia – the 'loss of flesh' that characterises most aging individuals. As originally defined by Rosenberg[117] in 1989, sarcopenia refers specifically to involuntary loss of skeletal muscle mass and consequently function. Although most commonly seen with advancing age, sarcopenia may result from a variety of processes, including biological changes of aging, disuse atrophy or unloading of muscle, and extrinsic factors including drugs and dietary intake patterns.

The clinical consequences of sarcopenia include muscle weakness, impaired gait and balance, falls and hip fractures, disability, immune dysfunction, insulin resistance, exacerbation of underlying diseases such as COPD and congestive heart failure, and an increased risk of mortality. Sarcopenia is often seen in concert with other adverse changes in body composition, such as decreased bone density and increased visceral fat mass, and in combination these shifts in body compartments may set the stage for metabolic syndrome (insulin resistance, hypertension, dyslipidaemia) beginning in middle age, as well as the functional limitations and disability of advanced age. The widespread prevalence of sarcopenia and the large burden of disease and disability it carries, along with the demographic trends predicting large increases in the oldest old age population (those over the age of 85 years), makes the

search for preventive and therapeutic strategies an urgent concern.[118]

Developing a suitable treatment for sarcopenia requires an understanding of its aetiology, which is not completely elucidated at present. Factors thought to be important include a reduction in anabolic hormone action (testosterone, estrogen, growth hormone, IGF-1, insulin resistance) with aging, decrease in protein synthesis capacity, loss of alpha motor neurone input, decreased protein and energy intake, decreased physical activity levels, as well as the onset of chronic disease and disability. Additionally, aging is associated with increased catabolic influences, including elevations of cortisol and cortisol response to stressors, leptin (associated with increased visceral fat stores), interleukin (IL)-6, IL-1β, and tumour necrosis factor-α.[118-120] Many of these pathways are inter-related and bidirectional. For example, decreases in physical activity level are associated with increased visceral fat deposition, which is in turn associated with decreased growth hormone and increased cortisol levels and resistance to the action of insulin, a milieu favouring sarcopenia. On the other hand, increased fat mass increases serum leptin that is directly catabolic for skeletal muscle, and may also lead to inactivity, subsequent reduced growth hormone secretion and accelerated sarcopenia via this indirect pathway as well.

Given the multitude of potential mediators of age-related sarcopenia, it is highly likely that more than one preventive or therapeutic approach will ultimately be necessary. Although oxandrolone has not yet been studied in sarcopenia, oxandrolone and other AASs are attractive candidates because they may influence a number of the abovementioned putative causal factors. Specifically, oxandrolone has been shown to:

- decrease visceral fat stores and total body fat;[39,40,42,57]
- increase protein synthesis rate in skeletal muscle;[20,26,28,57,62]
- increase dietary energy and protein intake;[12,39,48]
- improve nitrogen retention;[12,27,30,33,42]
- increase muscle function and physical activity levels;[35,36,42,48-52] and
- substitute for the losses of natural androgen and estrogen hormones.[121,122]

Although not yet proven, it is likely that losses of visceral fat would be associated with favourable reductions in catabolic influences such as basal and stress-related cortisol release, leptin levels, as well as improved growth hormone, IGF-1 and insulin action. Thus, one agent such as this, if shown to be effective and well tolerated over the long term, offers a highly desirable therapeutic profile for the syndrome of sarcopenia in the aged.

6. Conclusion

A variety of clinical conditions, as well as aging itself, are characterised by selective or preferential losses of muscle tissue, leading to functional impairment, exacerbation of underlying disease states and excess morbidity and mortality. There is a clear need to develop rational, effective and well tolerated therapeutic options for these conditions. Oxandrolone has several advantages relative to other anabolic steroids in this role, including:

- oral route of administration;
- high anabolic **:** androgenic potency; and
- lack of evidence of serious or irreversible hepatic toxicity.

Transient elevations of transaminase levels, as well as reductions in HDL cholesterol levels, are the most common adverse consequences seen in clinical trials, and appear to be readily reversible upon discontinuation of treatment. However, this adverse effect profile does raise concerns for any long-term treatment involving oxandrolone, particularly in individuals with other cardiovascular risk factors or underlying liver disease.

Virtually all of the oxandrolone studies reviewed provide evidence of clinically meaningful and statistically significant alterations in muscle, bone, fat, nutritional status, muscle function and status of underlying disease or recovery from acute catabolic insults. Very few data are currently available on the use of oxandrolone to combat the syndromes of sarcopenia and frailty in the elderly in general, al-

though emerging evidence from trials of testosterone supplementation in healthy elderly men suggest that this may be a fruitful avenue to pursue as well.[10] There is a clear need for an anabolic agent which would have utility in women as well as men; the far greater androgenic potency of testosterone limits its acceptability in women, and women constitute the largest proportion of very elderly frail individuals who might benefit from such treatment.

Before widespread clinical acceptance of AAS as a therapeutic option in medicine for treatment of sarcopenia or catabolic conditions, optimal risk : benefit ratios for oxandrolone and other agents in its class will need to be refined. This will require:

- long term studies (>1 year) of safety and efficacy in clinical populations;
- better titration of dosage to minimise adverse events;
- exploration of intermittent or short-term therapy rather than continuous exposure to these agents;
- combination with other complementary anabolic stimuli such as progressive resistance training, protein or energy supplementation;
- creation of a more favourable anabolic : catabolic milieu via simultaneous reduction of catabolic stimuli, such as cytokines, cortisol, stress, depression and visceral fat depots; and/or
- studies in women, particularly elderly women with current or impending disability.

The evidence base supporting the utility of oxandrolone to counteract catabolism in a wide spectrum of clinical populations, as well as age-related changes in body composition leading to disability, would be considerably strengthened by such research initiatives.

Given that we have found that the vast majority of studies of oxandrolone in various indications show significant improvement in body composition and functional recovery, we hope that this review may serve to stimulate further interest in this field. Oxandrolone has not yet been studied in sarcopenia, and such research would be of particular value.

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